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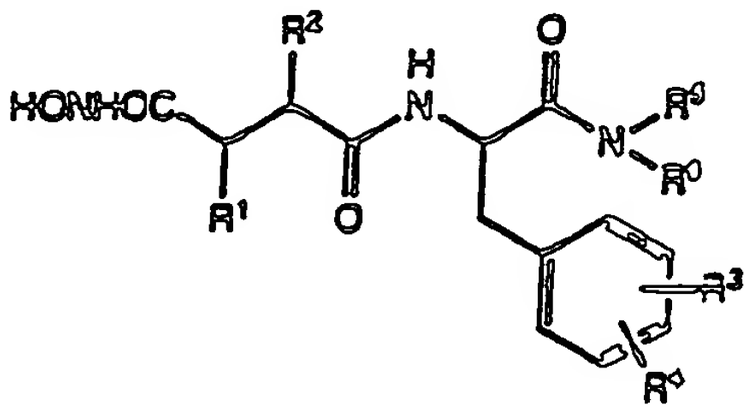
(54) Title: HYDROXAMIC ACID DERIVATIVES, PROCESS FOR THEIR PREPARATION AND USE THEREOF



(I)

(57) Abstract

Compounds of general formula (I): wherein R^1 is hydrogen, C_1-C_6 alkyl, phenyl, substituted phenyl, phenyl(C_1-C_6 alkyl), or heterocyclyl; or R^1 is ASO_nR^7 wherein A represents a C_1-C_6 hydrocarbon chain, optionally substituted with one or more C_1-C_6 alkyl, phenyl or substituted phenyl groups n = 0, 1, 2; R^7 is C_1-C_6 alkyl, phenyl, substituted phenyl, phenyl(C_1-C_6 alkyl), heterocyclyl, (C_1-C_6 alkyl)acyl thienyl or phenacyl; R^2 is hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, phenyl (C_1-C_6 alkyl) or cycloalkyl(C_1-C_6 alkyl); R^3 and R^4 are selected from hydrogen, halogen, cyano amino, amino(C_1-C_6)alkyl, amino di (C_1-C_6)alkyl, amino(C_1-C_6)alkylacyl, aminophenacyl, amino (substituted phenacyl, amino acid or derivative thereof, hydroxy, oxy(C_1-C_6)alkyl, oxyacyl, formyl, carboxylic acid, carboxamide, carboxy (C_1-C_6) alkylamide, carboxyphenylamide, carboxy(C_1-C_6) alkyl, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkyloxy(C_1-C_6) alkyl or acyloxy(C_1-C_6)alkyl, (C_1-C_6)alkylcarboxylic acid, (C_1-C_6) alkylcarboxy (C_1-C_6) alkyl, amino (C_{1-6})alkylacyl carboxylic acid or amino (C_{1-6})alkylacyl (C_{1-6}) alkylcarboxylate; or R^3 is OCH_2COR^8 R^4 is hydrogen; wherein R^8 is hydroxyl, C_1-C_6 oxyalkyl, C_1-C_6 oxyalkylphenyl, amino, C_1-C_6 aminoalkyl, C_1-C_6 aminodialkyl, C_1-C_6 aminoalkylphenyl, an amino acid or derivative thereof; or R^3 is $OCH_2CH_2OR^9$ and R^4 is hydrogen; wherein R^6 is C_1-C_6 alkyl, C_1-C_6 alkylphenyl, phenyl, substituted phenyl, (C_1-C_6 alkyl)acyl, or phenacyl; or R^3 is OCH_2CN and R^4 is hydrogen; R^5 is hydrogen or C_1-C_6 alkyl, or (C_1-C_6) alkylphenyl; R^6 is hydrogen or methyl; or a salt thereof; specifically excluded are compounds wherein: R^3 = R^4 = hydrogen or R^3 = R^4 = hydroxy or R^3 = hydrogen and R^4 = oxybenzyl or R^3 = hydrogen and R^4 = oxy(C_1-C_6 alkyl); or a salt thereof; have collagenase inhibition activity and are useful in the management of disease involving collagen degradation. Its uses include rheumatoid arthritis, corneal ulceration, osteoporosis, periodontitis, gingivitis and tumour invasion.

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Hydroxamic acid derivatives, process for their preparation and use thereof

A number of small peptide like compounds which inhibit metalloproteinase have been described. Perhaps the most notable of these are those relating to the angiotensin converting enzyme (ACE) where such agents act to blockade the conversion of the decapeptide angiotensin I to angiotensin II, a potent pressor substance. Compounds of this type are described in EP-A-0012401.

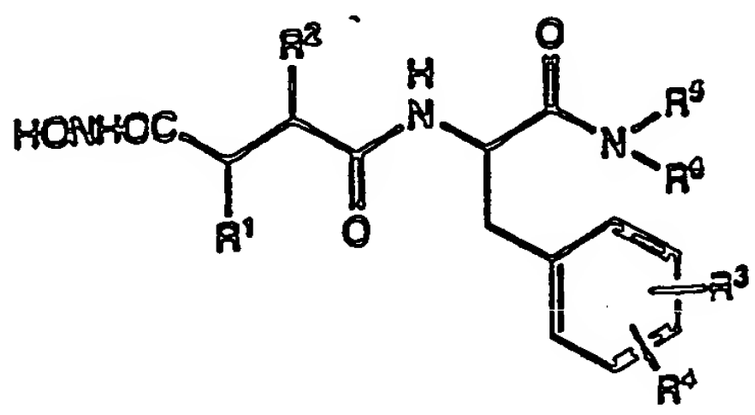
Certain hydroxamic acids have been suggested as collagenase inhibitor as in US-A-4 599 361, WO-A-9005716 and WO-A-9005719. Other hydroxamic acids have been prepared as ACE inhibitors, for example, in US-A- 4,105,789, while still others have been described as enkephalinase inhibitors as in US-A-4,495,540.

The hydroxamic acids of the current invention act as inhibitors of mammalian collagenase which initiates collagen breakdown. There is evidence implicating collagenase as one of the key enzymes in the breakdown of articular cartilage and bone in rheumatoid arthritis (Arthritis and Rheumatism, 20, 1231-1239, (1977)). Potent inhibitors of collagenase are useful in the treatment of rheumatoid arthritis and related diseases in which collagenolytic activity is important. These diseases include corneal ulceration, osteoporosis, periodontitis, gingivitis and tumour invasion.

The current invention relates to a series of hydroxamic

acids, which act as inhibitors of metalloproteinase, their preparation, pharmaceutical compositions containing them, and the intermediates involved in their preparation.

In a first aspect of the invention there is provided a compound of general formula I



I

Wherein :

R^1 is hydrogen, C_1 - C_6 alkyl, phenyl, substituted phenyl, phenyl(C_1 - C_6 alkyl), or heterocyclyl;

or R^1 is ASO_nR^7

wherein A represents a C_1 - C_6 hydrocarbon chain, optionally substituted with one or more C_1 - C_6 alkyl, phenyl or substituted phenyl groups

n = 0,1,2;

R^7 is C_1 - C_6 alkyl, phenyl, substituted phenyl, phenyl (C_1-C_6 alkyl), heterocyclyl, (C_1 - C_6 alkyl)acyl, thienyl or phenacyl;

R^2 is hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, phenyl (C_1 - C_6alkyl) or cycloalkyl(C_1 - C_6 alkyl);

R^3 and R^4 are selected from hydrogen, halogen, cyano amino, amino(C_1 - C_6)alkyl, amino di(C_1 - C_6)alkyl, amino(C_1 - C_6)alkylacyl, aminophenacyl, amino (substituted) phenacyl, amino acid or derivative thereof, hydroxy, oxy(C_1 - C_6)alkyl, oxyacyl, formyl, carboxylic acid, carboxamide, carboxy(C_1 - C_6) alkylamide, carboxyphenylamide, carboxy(C_1 - C_6) alkyl, hydroxy(C_1 - C_6)alkyl, (C_1 - C_6)alkyloxy(C_1 - C_6) alkyl or acyloxy(C_1 - C_6)alkyl, (C_1 - C_6)alkylcarboxylic acid, (C_1-C_6) alkylcarboxy(C_1 - C_6) alkyl, amino (C_{1-6})alkylacyl carboxylic acid or amino (C_{1-6})alkylacyl (C_{1-6}) alkylcarboxylate;

or R^3 is OCH_2COR^8 and R^4 is hydrogen;

wherein R^8 is hydroxyl, C_1 - C_6 oxyalkyl, C_1 - C_6 oxyalkylphenyl, amino, C_1 - C_6 aminoalkyl, C_1 - C_6 aminodialkyl, C_1 - C_6 aminoalkylphenyl, an amino acid or derivative thereof;

or R^3 is $OCH_2CH_2OR^9$ and R^4 is hydrogen;

wherein R^9 is C_1 - C_6 alkyl, C_1 - C_6 alkylphenyl, phenyl, substituted phenyl, (C_1 - C_6 alkyl)acyl, or phenacyl;

or R^3 is OCH_2CN and R^4 is hydrogen;

R^5 is hydrogen or C_1 - C_6 alkyl, or (C_1 - C_6) alkylphenyl;

R^6 is hydrogen or methyl;

or a salt thereof;

specifically excluded are compounds wherein:
$R^3 = R^4$ = hydrogen

or $R^3 = R^4$ = hydroxy

or R^3 = hydrogen and R^4 = oxybenzyl
or R^3 = hydrogen and R^4 = oxy(C_1 - C_6 alkyl).

Hereafter in this specification the term "compound" includes salt unless the context requires otherwise.

As used herein the term "C_1 - C_6 alkyl" refers to a straight or branched chain alkyl moiety having from one to six carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl and the like.

The term "C_2 - C_6 alkenyl" refers to a straight or branched chain alkyl moiety having two to six carbons and having in addition one double bond, of either E or Z stereochemistry where applicable. This term would include, for example, vinyl, 1-propenyl, 1- and 2-butenyl, 2-methyl-2-propenyl etc.

The term "cycloalkyl" refers to a saturated alicyclic moiety having from 3 to 8 carbon atoms and includes for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term 'heterocyclyl' refers to a saturated or unsaturated ring containing at least one hetero atom

such as nitrogen, oxygen or sulphur and includes for example, furan, pyrrole, thiophene, morpholine, pyridine, dioxane, imidazoline, pyrimidine and pyridazine.

The term "substituted", as applied to a phenyl or other aromatic ring, means substituted with up to four substituents each of which independently may be C_1-C_6 alkyl, C_1-C_6 alkoxy, hydroxy, thiol, C_1-C_6 alkylthiol, amino, halo (including fluoro, chloro, bromo and iodo), trifluoromethyl, nitro, -COOH, $-COONH_2$ or $-CONHR^A$, wherein R^A represents a C_1-C_6 alkyl group or the characteristic side chain of an amino acid such as alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, glycine, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine or histidine.

The term "amino acid" means one of the following R or S amino acids: glycine, alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, cysteine, methionine, asparagine, glutamine, lysine, histidine, arginine, glutamic acid and aspartic acid.

Derivatives of amino acids include acid halides, esters and substituted or unsubstituted amides, for example N methyl amide.

There are several chiral centres in the compounds according to the invention because of the presence of asymmetric carbon atoms.

The presence of several asymmetric carbon atoms gives rise to a number of diastereomers with the appropriate R or S stereochemistry at each chiral centre. The invention is understood to include all such diastereomers and mixtures thereof.

Preferred compounds include those in which, independently or in combination :

R^1 represents a hydrogen atom or a C_1 - C_4 alkyl, or phenyl group;

or R^1 represents ASO_nR^7 in which A is C_1 - C_4 hydrocarbon chain alkyl (for example methylene), n = 0, and R^7 is a phenyl, substituted phenyl or thienyl group;

R^2 represents a C_1 - C_5 alkyl (for example isobutyl) group;

R^3 represents cyano, aminoalkylacyl, amino (C_{1-6})alkylacylcarboxylic acid, amino (C_{1-6})alkylacyl (C_{1-6})alkylcarboxylate or OCH_2COR^8 and R^4 is hydrogen;

Wherein R^8 represents a hydroxyl group, C_1 - C_6 oxyalkyl, amino, C_1 - C_6 aminoalkylphenyl, C_1 - C_6 aminodialkyl, or an amino acid or derivative thereof;

R^5 represents a C_1 - C_4 alkyl (for example methyl) group;

R^6 represents a hydrogen atom.

Particularly preferred compounds include:

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxlic acid)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-N-methylamide)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-beta-alanine)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-(oxymethylcarboxy-glycine)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-N-benzylamide)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-cyano) phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-acetamido) phenylalanine-N-methylamide.

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxy-methylcarboxamide)-phenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio methyl succinyl]-L-(4-N-acetylamino)-phenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-methylsuccinyl]-L-(4-N-methylsuccinylamide)-phenyl-alanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthio-methyl)-succinyl]-L-(4-N-(methylsuccinylamide)-phenyl-alanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthio-methyl)-succinyl]-L-(4-N-(4-(4-oxobutanoic acid)-aminophenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenyl-thiomethyl)-succinyl]-L-(4-N-(methylsuccinylamido)-phenylalanine-N-methylamide;

[4-(N(hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenyl-thiomethyl)-succinyl]-L-(4-N-(4-(4-oxobutanoic acid)-aminophenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-methyl)-succinyl]-L-4-(oxymethylcarboxymethyl)-phenyl-alanine-N-methylamide.

[4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-methyl)-succinyl]-L-(4-N-(oxymethylcarboxylic acid)-phenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-methyl)-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-

methyl)-succinyl]-L-4-(oxymethylcarboxyglycine)-phenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-(3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycine)-phenylalanine-N-methyl-amide;

[4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-4-(oxy-methylnitrile)-phenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-(1-(2-methyoxycarbonyl)-ethyl)-4-methoxyphenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-(hydroxy-methyl)-4-methoxyphenylalanine-N-methylamide; or

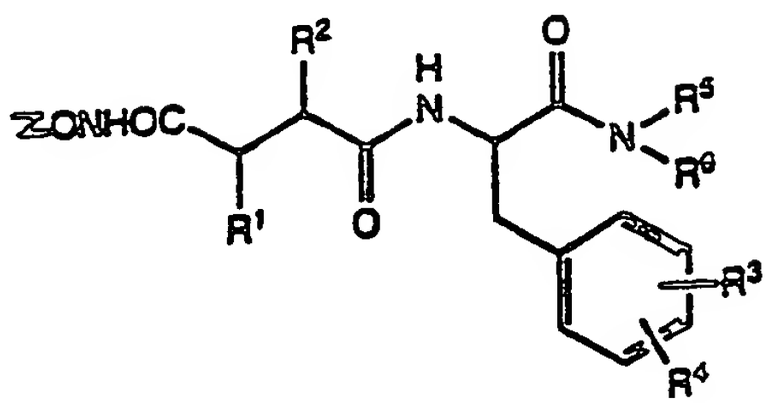
[4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-methyl-4-methyoxyphenylalanine-N-methylamide.

Compounds of the general formula I may be prepaped by any suitable method known in the art and/or by the following process, which itself forms part of the invention.

According to a second aspect of the invention, there is provided a process for preparing a compound of general formula I as defined above, the process comprising:

(a) deprotecting (for example by hydrogenation) a

compound of general formula II

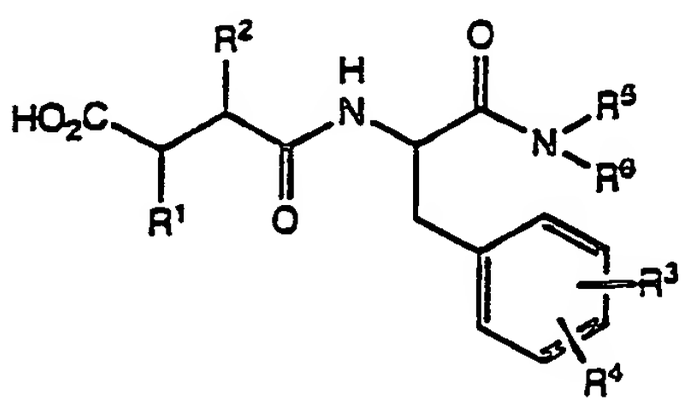


II

Wherein:

R^1, R^2, R^3, R^4, R^5 and R^6 are as defined in the general formula I and Z represents a suitable protective group (e.g. tert-butyl, tertbutylsilyl, benzyl or substituted benzyl);

(b) reacting a compound of general formula III



III

Wherein:

R^1, R^2, R^3, R^4, R^5, and R^6 are as defined in the general formula I,

with hydroxylamine or a salt thereof; and

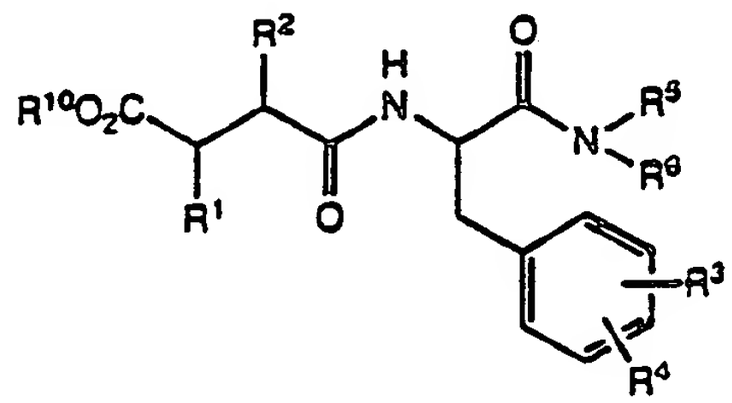
(c) optionally after step (a) or step (b) converting a compound of general formula I into another compound of general formula I.

Compounds of general formula I which are sulphoxide or sulphones can be derived from thio compounds of general formula I by oxidation. Alternatively, compounds of general formula II, or III which contain sulphur can be oxidised.

A compound of general formula II can be obtained by coupling, for example by conventional coupling techniques, a compound of general formula III with an O-protected hydroxylamine of formula NH_2OZ; wherein Z is as defined in general formula II.

A compound of general formula III can be prepared by

(a) de-esterifying (for example under acid or base catalysis) a compound of general formula IV

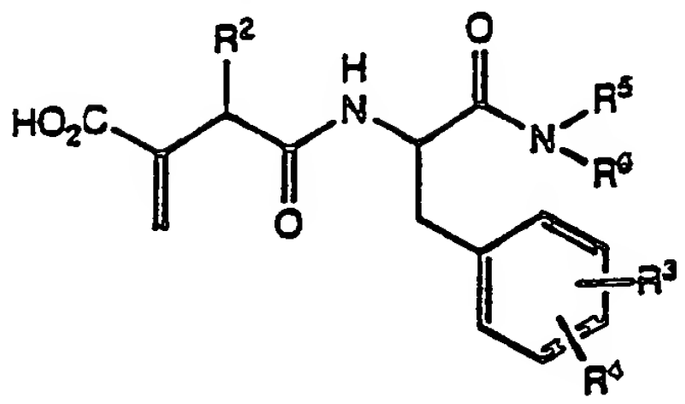


IV

Wherein:

R^1, R^2, R^3, R^4, R^5, and R^6 are as defined in the general formula I, and R^{10} represents a C_1 -C_6 alkyl or benzyl group; or

(b) by reacting a compound of general formula V



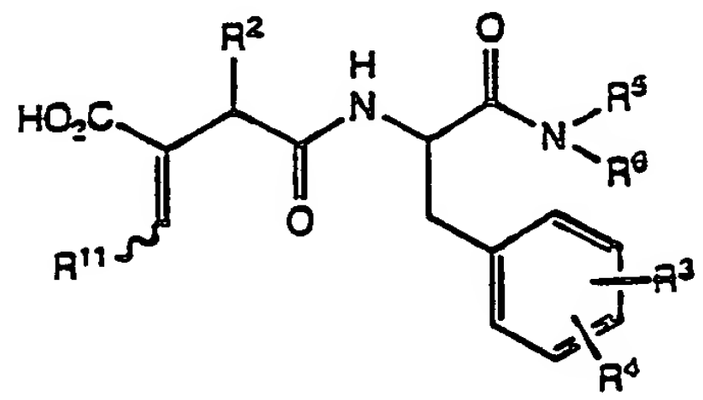
V

Wherein:

R^2, R^3, R^4, R^5, and R^6 are as defined in the general formula I,

either with a thiol of general formula R^7SH, wherein R^7 is as defined in general formula I, to give a compound of general formula III in which R^1 is ASO_nR^7, A represents a methylene group and n is 0.

or with compound R^1X where R^1 is benzyl or substituted benzyl and X is F, Cl, Br of I in the presence of a palladium catalyst to provide a compound of general formula VI



VI

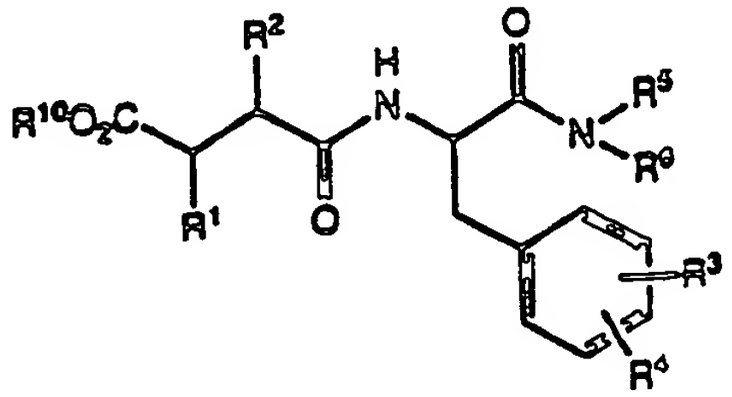
Wherein:

R^2, R^3, R^4, R^5, and R^6 are as defined in the general formula I, and R^1 is benzyl or substituted benzyl, which may be converted to a compound of general formula III wherein R^2 is benzyl or substituted benzyl,

by hydrogenation; or

(c) by converting a compound of general formula III into another compound of general formula III.

A compound of general formula V can be prepared from a compound of general formula IV



IV

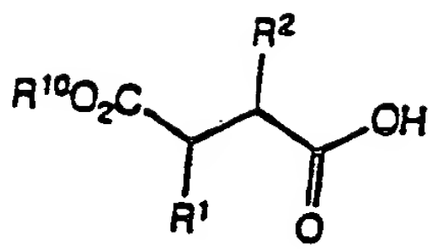
Wherein:

R^2, R^3, R^4, R^5, and R^6 are as defined in the general formula I, R^1 is carboxybenzyl or carboxy (C_1 - C_6) alkyl and R10 is benzyl or (C_1 -C_6) alkyl, and R^{10} is benzyl or (C_1 - C_6) alkyl,

by de-esterification (for example by hydrogenation) followed by reaction with formaldehyde in the presence of morpholine.

A compound of general formula IV can be prepared

(a) By reacting, for example by conventional coupling techniques, an acid of formula VII, or an activated ester derivative thereof,

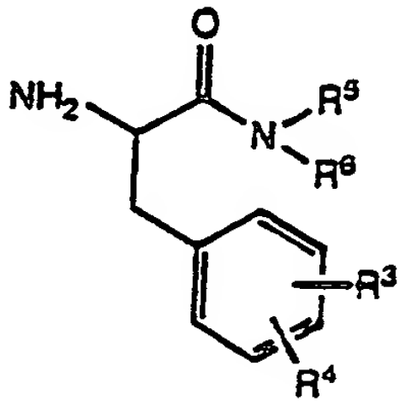


VII

Wherein:

R^1 and R^2 are as defined in the general formula I, and R^{10} is as defined above.

with an amine of general formula VIII



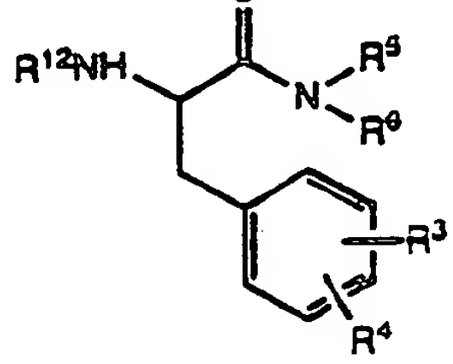
VIII

Wherein:

R^3, R^4, R^5, and R^6 are as defined in the general formula I;

(b) by converting a compound of general formula IV into another compound of general formula IV.

An amine of general formula VIII can be prepared by deprotection (for example with trifluoroacetic acid) of a compound of general formula IX

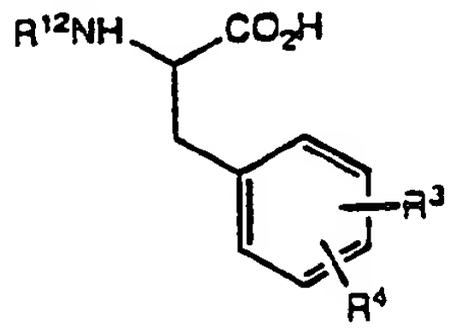


IX

Wherein:

R^{12} is a conventional amine protecting group and R^3, R^4, R^5 and R^6 are as defined in general formula I.

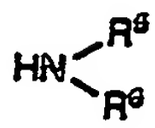
A compound of general formula IX may be prepared by coupling an acid of general formula X



X

Wherein:

R^3 and R^4 , are defined as in general formula I, with an amine of general formula XI



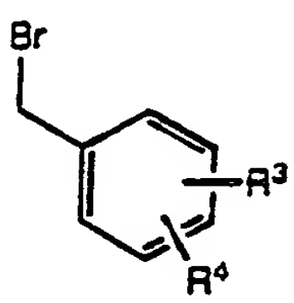
XI

Wherein:

R^5 and R^6 are as defined in general formula I

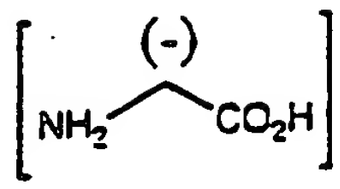
A compound of general formula X may be prepared

(a) by reaction of an aryl halide of general formula XII



XII

Wherein R3 and R4 are as defined in general formula I with a glycinate anion equivalent of formula XIII

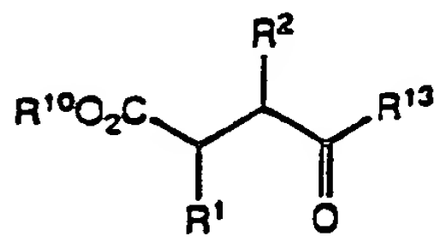


XIII

followed by acid hydrolysis, protection of the amino function and base catalysed release of the carboxylic acid; or

(b) by converting a compound of general formula X to another compound of general formula X.

A compound of general formula VII may be prepared by reaction of a compound of general formula XIV



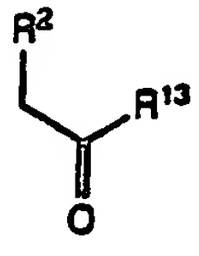
XIV

Wherein:

R^2 is as defined in the general formula I, R^1 is hydrogen, R^{10} is as described above and R^{13} is a chiral auxillary for example as described by Evans (J. Amer. Chem. Soc., 104, 1737, (1982)).

with lithium hydroxide/hydrogen peroxide.

A compound of general formula XIV may be produced by alkylation of the anion of a compound of general formula XV

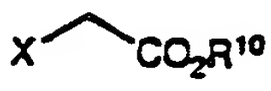


XV

Wherein:

R^2 is as defined in the general formula I and R^{13} is a chiral auxillary,

with an alkylating agent of general formula XVI.



XVI

Wherein:

R^{10} is as described above and X is a leaving group, for example bromide, iodide or triflate.

Compounds of general formulae XI, XII, XIII, XV and XVI and other reagents are either available commercially or can be synthesised by simple chemical procedures.

The potency of compounds of the present invention to

act as inhibitors of collagenase was determined by the procedure of Cawston and Barrett, (Anal. Biochem., 99, 340 -345, 1979) whereby a 1mM solution of the inhibitor being tested or dilutions thereof is incubated at 37°C for 16 hours with collagen and collagenase (buffered with Tris HCl - $CaCl_2$; pH 7.6). The collagen is acetylated ^{14}C collagen prepared by the method of Cawston and Murphy (Methods in Enzymology, 80, 711, (1981)). The samples are centrifuged to sediment undigested collagen and an aliquot of the radioactive supernatant removed for assay on scintillation counter as a measure of hydrolysis. The collagenase activity in the presence of 1 mM inhibitor, or a dilution thereof, is compared to activity in a control devoid of inhibitor and the results reported as that inhibitor concentration effecting 50% inhibition of the collagenase.

In a further aspect of the invention there is provided the use of a compund of general formula I in medicine, particularly in a method of treatment of diseases in which collagenolytic activity is important.

In another aspect of the invention there is provided the use of a compound of general formula I in the preparation of an agent for the treatment of diseases in which collagenolytic activity is important.

The invention also provides a pharmaceutical composition comprising one or more compounds of general formula I in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants. Other active ingredients

may also be included in the compositions of the invention.

The compositions of the present invention may be formulated for administration by any route depending on the disease being treated. The compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parental solutions or suspensions.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients. Examples of these are binding agents such as syrup, acacia, gelatin, sorbitol, tragacanth, and polyvinylpyrollidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium sterate, talc, polyethylene glycol or silica; disintegrants, for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup,gelatin, hydrogenated edible fats; emulsifiying agents, for example lecithin, sorbitan monooleate, or acacia;

non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

The dosage unit involved in oral administration may contain from about 1 to 250 mg, preferably from about 25 to 250 mg. A suitable daily dose for a mammal amy vary widely depending on the condition of the patient. However, a dose of about 0.1 to 300mg/kg body weight, particularly from about 1 to 100 mg/kg body weight may be appropriate.

For topical application to the skin the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics such as the British Pharmacopoeia.

For topical applications to the eye, the drug may be made up into a solution or suspension in a suitable sterile aqueous or non-aqueous vehicle. Additives, for instance buffers such as sodium metabisulphite or disodium edeate; preservatives including bactericidal and fungicidal agents, such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorohexidine, and thickening agents such as hypromellose may also be included.

The dosage employed for the topical administration

will, of course, depend on the size of the area being treated. For the eyes each dose will be typically in the range from 10 to 100 mg of the drug.

The active ingredient may also be administered parenterally in a sterile medium. The drug depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anaesthetic, preservatives and buffering agents can be dissolved in the vehicle.

For use in the treatment of rheumatoid arthritis the compounds of this invention can be administered by the oral route or by injection intra-articularly into the affected joint. The daily dosage for a 70 kg mammal will be in the range of 10 mgs to 1 gram.

The following examples illustrate the invention, but are not intended to limit the scope in any way.

The following abbreviations have been used in the Examples:DCM - Dichloromethane
DMF - N,N-Dimethylformamide
HOBT - Hydroxybenztriazole
NMM - N-Methylmorpholine
TFA - Trifluoroacetic acid
THF - Tetrahydrofuran
WSCDI - N-(Dimethylaminoethyl)-N'-ethylcarbodiimide.

EXAMPLES

Example 1

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxylic acid)-phenylalanine-N-methylamide

Example 1a

N-(4-Methylpentanoyl)-4S-phenylmethyl-2-oxazolidinone

A dry 500 ml flask equipped with a magnetic stirrer was charged with (S)-4-Phenylmethyl-2-oxazolidinone (17.72g, 0.1 mol), this was capped with a rubber septum and flushed with N_2. Anhydrous THF (300 ml) was added via cannula and the resulting solution was cooled to -78°C in an acetone/dry ice bath. A solution of 1.47M n-butyllithium in hexane (68.4 ml, 0.101 mol) was transferred via cannula to a dry, septum-stoppered 100 ml dropping funnel. This was added dropwise to the THF solution over 10 minutes.

4-methyl valeric acid chloride (14.80g 0.11 mol) was added in one portion by syringe after completion of the addition of n-butyllithium. The resulting solution was stirred at -78°C for 30 minutes and then allowed to warm to ambient temperature over 30 minutes. Excess of the acid chloride was quenched by the addition of aq. NH_4Cl (60 ml) and the bulk of the solvent was removed. The resulting slurry was extracted with dichloromethane (2 x 80 ml). The combined organic extracts were washed with 1M NaOH (75 ml), brine (75 ml), dried (Na_2SO_4 anhyd.) and filtered. The solvent was removed to yield

a yellow oil (29.20g, 106%).

Analysis calculated for $C_{16}H_{21}NO_3$ MWt = 275.34

$delta_H$ (250 MHz, $CDCl_3$), 0.97 (6H, d, $C(CH_3)2$, J=6.2 Hz), 1.53-1.76 (3H, m, CH_2CHMe_2), 2.78 (1H, dd, CH_2Ph, J=9.5 Hz), 2.85-3.05 (2H, m, $COCH_2$) 3.30 (1H, dd, CH_2Ph, J=3.3 Hz) 4.16-4.25 (2H, m, CH_2OCO) 4.63-4.73 (1H, m, CHBnz) 7.19-7.34 (5H, m, C_6H_5)

Example 1b

N(4-(t-Butoxy)-2R-isobutylsuccinyl)-4S-phenylmethyl-2-oxazolidinone

N-(4-Methylpentanoyl)-4S-phenylmethyl-2-oxazolidinone (20g, 0.0726 mol) was placed in a dry 1 litre 3-necked flask to which was added dry THF (400 ml). The mixture was kept under a stream of Argon and cooled to -78°C (dry ice/acetone). Sodium hexamethyldisilylamide (1M solution in THF, 0.0726 mol, 72.6 ml) was added dropwise through a dropping funnel (it was added to the funnel via syringe). After stirring for 20 minutes, t-butylbromoacetate (21.02g, 15.8 ml, 0.1089 mol, 1.5 equiv.) was added dropwise over 1 minute, to give an orange solution. The mixture was kept at -78°C and allowed to warm to -50°C over 2 hours (after which time it turned pink). The reaction was then quenched by adding acetic acid (10.90g, 10.4 ml, 0.1815 mol, 2.5 equiv.) in ether (50 ml) at -50°C whereupon the solution became colourless. The solvent was removed and the resulting slurry partitioned between ethyl acetate and brine. The ethyl acetate layer was washed

once with brine and the original brine layer was back-extracted with ethyl acetate. The combined organic layers were dried and the solvent removed, giving a yellow oil which crystallised on cooling overnight to yield the title compound as a crystalline solid (21.36g, 76%).

Analysis calculated for $C_{22}H_{31}O_5N$ MWt = 389.48

$delta_H$ (250 MHz, $CDCl_3$) 0.91-0.96 (6H, dd, CMe_2, J=4.5 Hz), 1.44 (9H, s, CMe_3) 1.24-1.72 (3H, m, CH_2CHMe_2), 2.49 (1H, dd, CH_2Ph, J=4.6 Hz), 2.72 (1H, dd, $CH_2CO_2CH(CH_3)_3$, J=2.3 Hz), 3.36 (1H, dd, CH_2Ph, J=3.25 Hz), 4.16-4.18 (2H, m, CH2OCO), 4.20-4.35 (1H, m, CH-CO), 4.62-4.72 (1H, m, CHBz), 7.24-7.38 (5H, m, C_6H_5)

$[alpha]^{25}D$ = + 66.9 (c=1, MeOH)

Example 1c

4-(t-Butoxy)-2R-isobutylsuccinic acid

N(4-(t-Butoxy)-2R-isobutylsuccinyl)-4S-phenylmethyl-2--oxazolidinone (15.30g, 0.039 mol) was placed in a 1 litre flask with a stirrer bar and to it was added 750 ml of 4.1 THF:H_2O. This solution was stirred and cooled to 0°C (ice/acetone bath) then 60% aq. H_2O_2 (4.5 ml, 0.157 mol, 4 equiv) was added via syringe over 5 mins, followed by $Li(OH)_2$ (2.65g, 0.063 mol, 1.6 equiv.) in 100 ml water. The reaction mixture was stirred for 1h at 0°C. TLC (10% methanol/dichloromethane) showed complete reaction (product gave a yellow spot on TLC on staining with bromocresol green and heating). The reaction mixture was quenched with $NaNO_2$ (10.88g, 0.157 mol, 4 equiv.), the final pH was 12-13. THF was removed in-vacuo and the aqueous layer extracted with dichloromethane (3 x 200 ml) to recover the chiral auxliary. The organic extracts were dried ($MgSO_4$ anhyd.), solvent removed in-vacuo and the resulting solid chiral auxiliary (7.05g, 0.039 mol, 100%) recrystallised from ethyl acetate/hexane (2:1)

[alpha]^{25}D = 13.0° (x=1, MeOH)

[alpha]^{25}D 4.9° (c=1, EtOH)

The aqueous layer was cooled in an ice bath and acidified to pH 5-6 with 2M HCl. The resulting cloudy solution was extracted with ethyl acetate (4 x 200 ml), readjusting the pH to 5-6 in between extractions. The combined organic extracts were dried over $MgSO_4$,

filtered and the solvent was removed to yield the title compound as a pale yellow oil (8.21g, 91%).

$delta_H$ (250 MHz, $CDCl_3$) 0.93 (6H, dd, J=7, 8Hz), 1.28 (1H, m), 1.64 (1H, m), 2.38 (1H, dd, J=16, 5Hz), 2.59 (1H, dd, J=16, 9Hz), 2.85 (1H, m).

$[alpha]^{25}D$ = + 10.4 (c=1, MeOH)

Example 1d

Pentafluorophenyl 4-(t-butoxy)-2R-isobutylsuccinate

A solution of the chiral acid (from example 1c, 5.0g, 21.7 mmol) and pentafluorophenol (8.0g, 43 mmol) in dichloromethane (50 ml) was cooled to 0°C before dropwise addition of N-methylmorpholine (2.7g, 26.7 mmol) followed by water-soluble carbodiimide (5.5g, 28.7 mmol) in several portions. After the WSCDI had dissolved, a small amount of white insoluble material remained which did not dissolve on addition of N,N-dimethylformamide (5 ml). The mixture was allowed to warm to room temperature and was then stirred overnight at room temperature.

Solvents were removed on a rotary evaporator and the residue was resuspended in dichloromethane (100 ml) and washed successively with 1M HCl (2 x 200 ml), 0.5M Na_2CO3 (2 x 200 ml) and brine (200 ml) and dried (Na_2SO_4). TLC (CH_2Cl_2) showed a single UV-active spot ($R_f$ca.0.8) with a small amount of brown baseline impurity. The solution was therefore evaporated to a brown oil and flushed through a silica column (2 x 20

cm) with dichloromethane. UV-positive fractions were pooled and evaporated to give the pentafluorophenol ester as a pale yellow oil (8.31g, 97%).

$C_{18}H_{21}F_5O_4$ MWt = 396.35

i.r. (neat) 1785, 1732 cm^{-1}

$delta_H$ (250 MHz, $CDCl_3$) 3.23 (1H, m), 2.74, 2.52 (2H, ddd, J=9.3, 5.2, 16.8 Hz), 1.75 (2H, m), 1.46 (10H, s and m), 0.98, 0.96 (6H, 2d, J=6.6 Hz)

$delta_C$ (250 MHz, $CDCl_3$) 171.3, 170.3, 143.2-138.9, 81.4, 41.0, 39.5, 37.7, 28.0, 25.8, 22.6, 22.1

Example 1e

O-Benzyl-L-tyrosine N-methylamide

N-Boc-O-benzyl tyrosine methylamide (5.29g, 13.8 mmol) was taken up in CH_2Cl_2 (100 ml). To the solution at 0^oC TFA (10 ml) was added dropwise and the solution allowed to warm to ambient temperature. After 4 hours the solvent and TFA were removed under vacuum. Any remaining TFA was quenched with saturated $NaHCO_3$ solution (100 ml). The reaction mixture was extracted using CH_2Cl_2 (100 ml) and washed with saturated $NaHCO_3$ solution (100 ml) and brine (100 ml). The CH_2Cl_2 layer was dried over Na_2SO_4 and the solvent was removed under vacuum to give a white solid, which was recrystallised from ethyl acetate/hexane to yield the title compound as a white crystalline solid (3.35g, 85.4%).

delta$_H$ (250 MHz, $CDCl_3$) 7.45-7.33 (5H, bm, Bn-H), 7.23 (1H, bs, CONHMe), 7.13 (2H, d, J=8.5 Hz, Ar-H), 6.93 (2H, d, J= 8.6 Hz, Ar-H), 5.06 (2H, s, CH_2), 3.56 (1H, dd, J=5.1, 4.0 Hz, CH), 3.20 (1H, dd, J=9.8, 4.0 Hz, H of CH_2), 2.82 (3H, d, J=5.0 Hz, NHCH$_3$), 2.65 (1H, dd, J=9.3, 4.5 Hz, H of CH_2), 1.35 (2H, bs, NH_2).

Example 1f

[4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-benzyloxy) phenylalanine-N-methylamide

To a stirred solution of the O-benzyl-L-tyrosine-N-methylamide (from example 1e, 3g, 10.6 mmol) in DMF (100 ml) was added the chiral pentafluorophenyl ester (from example 1d, 8.37g, 21.1 mmol). The resulting solution was stirred at room temperature overnight. The DMF was removed under vacuum. The residue was taken up in CH_2Cl_2 (200 ml) and washed with saturated $NaHCO_3$ (2 x 100 ml), citric acid (2 x 100 ml) and brine (100 ml). The organic layer was dried over $MgSO_4$ and the solvent removed under vacuum to give a clear oil. Flash chromatography (flash silica, CH_2Cl_2 to 5% MeOH/CH2Cl2) gave the title compound as a pale yellow solid (4.95g, 94%).

$C_{29}H_{40}N_2O_5$MWt = 496.65

delta$_H$ (250 MHz, $CDCl_3$) 7.45-7.31 (5H, m, CH-21 to 25), 7.15 (2H, d, J=8.6 Hz, CH-9,11), 6.91 (2H, d, J=8.6 Hz, CH-8,12), 6.30 (1H, d, J=7.8 Hz, CONH), 5.92 (1H, m, CONHMe), 5.04 (2H, s, CH_2-19), 4.50 (1H, q, J=7.8 Hz, CH-5), 3.10 (1H, dd, J=6.3, 6.2 Hz, CH_2-6a), 2.82 (1H,

dd, J=7.8 Hz, CH_2-6b), 2.70 (3H, d, J=4.8Hz, CH_3-13), 2.61 (1H, m, CH-3), 2.46 (2H, m, CH_2-2a, 2b), 1.52 (2H, m, 1.44, CH_2-15), (9H, s, CH_3-27, 28, 29), 1.19 (1H, m, CH-16), 0.88, 0.85 (6H, 2d, J=6.5, 6.3 Hz, CH_3-17, 18).

Example 1g

[4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-hydroxy)-phenylalanine-N-methylamide

[4-(t-Butoxy)-2R-isobutylsuccinyl)-L-(4-benzyloxy) phenylalanine-N-methylamide (2.19g, 4.4 mmol) was taken up in 10% cyclohexene/ethanol (30 ml) and 10% Pd/charcoal (0.219g) added. The mixture was then heated under reflux. After 3 hours the hot solution was filtered through glass fibre paper and the black solid washed with methanol. The filtrate was concentrated under reduced pressure to give the title compound as a white foam (1.78g, 99%).

$C_{22}H_{34}N_2O_5$ MWt = 405.6

$delta_H$ (250 MHz, $CDCl_3$) 7.08 (2H, d, J=8.6 Hz, CH-9, 11), 6.76 (2H, d, J=8.6 Hz, CH-8, 12), 6.35 (1H, d, J=8.0 Hz, CONH), 5.91 (1H, m, CONHMe), 4.50 (1H, q, J=7.9 Hz, CH-5), 3.06 (1H, dd, J=6.2Hz, CH_2-6a), 2.96 (1H, dd, J=7.9 Hz, CH_2-6b), 2.71 (3H, d, J=4.8 Hz, CH_3-13), 2.61 (1H, m, CH-3), 2.48 (2H, m, CH_2-2a, 2b), 1.52 (2H, m, CH_2-15), 1.44 (9H, s, CH_3-20, 21, 22), 1.25 (1H, m, CH-16), 0.86 (6H, d, J=6.4 Hz, CH_3-17, 18).

$delta_C$ (250 MHz, $CDCl_3$) 173.8, 170.4, 154.2, 128.8,

126.3, 114.2, 79.8, 76.1-75.1, 53.7, 39.6, 36.7, 36.1, 26.6, 24.8, 24.2, 21.2, 20.9.

Example 1h

[4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-carboxybenzyl)-phenylalanine-N-methylamide

[4-(t-Butoxy)-2R-isobutylsuccinyl)-L-(4-hydroxy) phenylalanine-N-methylamide (2.69g, 6.6 mmol) was taken up in dry acetone (150 ml). Anhydrous Na_2CO_3 (0.84g, 7.9 mmol) was added with stirring, followed by dropwise addition of benzyl-2-bromoacetate (2.27g, 9.9 mmol). The reaction flask was flushed with argon and then the reaction mixture heated under reflux. After 48 hours the solvent was removed under vacuum. The residue was taken up in CH_2Cl_2 (100 ml) washed with saturated Na_2CO_3 (100 ml), 1M HCl (100 ml) and brine (100 ml), dried over $MgSO_4$ and the CH_2Cl_2 removed under vacuum to give a yellow oil. Flash chromatography (flash silica, 2% MeOH/CH_2Cl_2) gave the title compound as a white solid (1.91g, 52%).

$C_{31}H_{42}N_2O_7$ MWt = 554.69

$delta_H$ (250 MHz, $CDCl_3$) 7.36 (5H, s, CH-23-27), 7.14 (2H, d, J=8.7 Hz, CH-9, 11), 6.83 (2H, d, J=8.7 Hz, CH-8, 12), 6.33 (1H, d, J=7.9 Hz, CONH), 5.92 (1H, m, CONHMe), 5.24 (2H, s, CH_2-21), 4.64 (2H, s, CH_2-19), 4.48 (1H, m, CH-5), 3.08 (1H, dd, J=6.2 Hz, CH_2-6a), 2.96 (1H, dd, J=7.9 Hz, CH_2-6b), 2.68 (3H, d, J=4.8 Hz, CH_3-13), 2.63 (1H, m, CH-3, 2.46 (2H, m, CH_2-2a,2b),

1.48 (2H, m, CH_2-15), 1.43 (9H, s, CH_3-29, 30, 31), 0.87, 0.84 (6H, 2d, J=6.5 Hz, CH_3-17,18).

Example 1i

[4-Hydroxy-2R-isobutylsuccinyl]-L-(4-oxymethyl-carboxybenzyl)-phenylalanine-N-methylamide

[4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-carboxybenzyl)-phenylalanine-N-methylamide (2.12g, 3.8 mmol) was taken up in 95% TFA/H_2O (50 ml). The solution was stirred at 0°C for 3 hours. TFA/H_2O removed under vacuum. The residue was taken up in CH_2Cl_2 (50 ml) washed with brine (3 x 50 ml) dried over $MgSO_4$ and the solvent removed under vacuum to give the title compound as a white solid (1.89g, 99%).

Example 1j

[4-(N-benzyloxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxybenzyl)-phenylalanine-N-methylamide

[4-Hydroxy-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy--benzyl)-phenylalanine-N-methylamide (1.89g, 3.79 mmol) was dissolved in CH_2Cl_2 (20 ml). To the solution was added HOBT (0.63g, 4.17 mmol), WSCDI (1.09g, 5.6 mmol), NMM (0.58g, 5.6 mmol) and after 15 minutes benzylhydroxylamine (0.51g, 4.17 mmol). The reaction mixture was stirred at room temperature. After 16 hours the solvent was removed. The yellow residue was taken up in ethyl acetate whereupon white crystals precipitated out, which were collected by filtration and washed with ethyl acetate to yield the title

compound as a white solid (0.58g, 27%).

$C_{34}H_{41}N_3O_7$ MWt = 603.72

$delta_H$ (250 MHz, $CDCl_3$) 8.59, (1H, m, CONHOBz), 7.37 (10H, s, CH-23-27, CH-30 to 34), 7.11 (2H, d, J=8.6 Hz, CH-9, 11), 6.80 (2H, d, J=8.6 Hz, CH-8,12), 6.47 (1H, m, CONH), 5.95 (1H, m, CONHMe), 5.21 (2H, s, CH_2-21), 4.87 (2H, m, CH_2-28), 4.63 (2H, s, CH_2-19), 4.52 (1H, m, CH-5), 3.02 (2H, m, CH_2-6a, 6b), 2.71 (3H, d+m, J=4.8 Hz, CH_3-13, CH-3), 2.42 (2H, m, CH_2-2a, 2b), 1.46 (2H, m, CH2-15), 1.18 (1H, m, CH-16), 0.87, 0.84 (6H, 2d, J=6.8, 6.6 Hz, CH_3-17,18).

Example 1k

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxylic acid)-phenylalanine-N-methylamide

[4-(N-benzyloxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxybenzyl)-phenylalanine-N-methylamide (467 mg, 0.77 mmol) was taken up in 10% cyclohexene/ethanol (40 ml) and 20% Pd/charcoal (93 mg) added with stirring. The solution was heated under reflux and after 3 1/2 hours the solution filtered through glass fibre paper. The filtrate was concentrated down under reduced pressure to give the title compound as a white solid (322 mg, 98%).

mpt = 168°C

Analysis calculated for $C_{20}H_{29}N_3O_7$ MWt= 423.7

Requires C 56.73 H 6.90 N 9.92

Found C 56.52 H 6.91 N 9.59

$delta_H$ (250 MHz, MeOD) 7.89 (1H, bd, CONHMe), 7.11 (2H, d, J=8.4 Hz, CH-9,11), 6.81 (2H, d, J=8.4 Hz, CH-8.12), 4.56 (2H, s, CH_2-19), 4.44 (1H, m, CH-5), 3.05 (1H, dd, J=6.4, 6.3 Hz, CH_2-6a), 2.87 (1H, dd, J=8.8, 9.0 Hz, CH_2-6b), 2.64 (3H, s,CH_3-13), 2.78-2.58 (1H, bm, CH-3), 2.16 (1H, dd, J=4.7, 7.8 Hz, CH-2a), 2.04 (1H, dd, J=6.5, 6.6 Hz, CH-2b), 1.36 (2H, m, CH2-15), 1.13 (1H, m, CH-16), 0.81, 0.77 (6H, 2d, J=6.3 Hz, CH_3-17, 18).

$delta_C$ (250 MHz, DMSO) 173.34, 170.93, 169.80, 167.17, 155.8, 130.2, 129.5, 113.5, 64.1, 53.7, 40.4, 40.2, 40.0, 38.03, 35.86, 35.16, 25.10, 24.63, 22.78, 21.41.

Example 2

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-N-methylamide)phenylalanine-N-methylamide

Example 2a

[4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-carboxylic acid)-phenylalanine-N-methylamide

Utilising the procedure described in example 1g but employing [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxybenzyl)-phenylalanine-N-methylamide (from example 1h, 9.90 g, 17.85 mmol) in lieu of [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-benzyloxy)-phenylalanine-N-methylamide yielded, the title compound as a white solid (8.07 g, 97.3%)

$delta_H$ (250 MHz, $CDCl_3$) 7.07 (2H, d, J=8.6 Hz, CH-9, 11), 7.03 (1H, m, CONHCH), 6.79 (2H, d, J=8.6 Hz, CH-8,12), 6.70 (1H, m, CONHMe), 4.63 (1H, m, CH-5), 4.60 (2H, s, CH2-19), 2.96 (2H,d, J=7.1 Hz, CH_2-6), 2.66 (3H, d, J=4.8 Hz, CH_3-13), 2.65 (1H, s, CH-3), 2.65 (1H, s, CH-3), 2.43 (1H, dd, J=8.5 Hz, CH_2-2a), 2.33 (1H, dd, J=5.3 Hz, CH2-2b), 1.45 (2H, m, CH_2-15), 1.41 (9H, s, CH3-21,22,23), 1.20 (1H, m, CH-16), 0.82 (6H, dd, J=6.3, 6.2 Hz, CH_3-17,18).

$delta_C$ (250 MHz, $CDCl_3$) 174.1, 170.7, 170.2, 155.3,

128.9, 128.4, 113.3, 79.6, 76.1-75.1, 63.7, 53.4, 39.8, 39.6, 36.7, 35.8, 26.6, 24.8, 24.2, 21.3, 20.8.

Example 2b

[4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-carboxy-N-methylamide)-phenylalanine-N-methylamide

[4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-carboxylic acid)-phenylalanine-N-methylamide (0.5g, 1.07 mmol) was dissolved in CH_2Cl_2 (100 ml). At 0°C pentafluorophenol (0.4g, 2.15 mmol), WSCDI (0.26g, 1.3 mmol) and N-methylmorpholine (0.11g, 1.1 mmol) were added. After 15 minutes 8M methylamine in ethanol (0.25g, 2.7 mmol) was added dropwise. The solution was allowed to warm to ambient temperature and stirred for 12 hours. A white solid of $MeNH_2$.HCl precipitated out, but was not collected. The reaction solution was washed with 1M HCl (100 ml), 1M Na_2CO_3 (100 ml) and brine (100 ml). The CH_2Cl_2 layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to give the title compound as a white solid (0.44g, 86%).

$delta_H$ (250 MHz, CDCl3) 7.19 (2H, d, J=8.6 Hz, CH-9, 11), 6.84 (2H, d, J=8.6 Hz, CH-8,12), 6.60 (1H, m, CONHMe), 6.27 (1H, d,J=7.8 Hz, CONH), 5.99 (1H, m, CONHMe), 4.52 to 4.46 (3H, s+q, CH-5, CH_2-19), 3.09 (2H, m, CH_2-6a,6b), 2.92 (3H, d, J=4.8 Hz, CH3-21), 2.72 (3H, d, J=4.8 Hz, CH_3-13), 2.61 (1H, m, CH-3), 2.46 (2H, m, CH_2-2a, 2b), 1.45 (11H, s+m, CH_3-23, 24, 25, CH_2-15) 1.20 (1H, m, CH-16), 0.87, 0.84 (6H, 2d, J=6.3 Hz, CH_3-17,18).

Example 2c

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-N-methylamide)phenylalanine-N-methylamide

The title compound was prepared from [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-N-methylamide)-phenylalanine-N-methylamide utilising the method described in examples 1i to 1k

mpt = 211°C

Analysis calculated for $C_{21}H_{32}N_4O_6$ MWt = 436.51

Requires C 57.78 H 7.39 N 12.84

Found C 57.30 H 7.27 N 12.56

$delta_H$ (250 MHz, DMSO) 10.39 (1H, s, CONHOH), 8.74 (1H, s, CONHOH), 7.98 (2H, m, CONHMe), 7.85 (1H, d, J=4.7 Hz, CONH), 7.12 (2H, d, J=8.5 Hz, CH-9,11), 6.83 (2H, d, J=8.6 Hz, CH-8,12), 4.38 (2H, s, CH-19), 4.32 (1H, m, CH-5), 2.96 (1H, dd, J=5.1, 5.0 Hz, CH_2-6a), 2.74 (1H, dd, J=9.6, 9.7 Hz, CH_2-6b), 2.64 (3H, d, J=4.7 Hz, CH_3-21), 2.60 (1H, m, CH-3), 2.55 (3H, d, J=4.5 Hz, CH_3-13), 2.05 (1H, dd, J=3.7, 7.0 Hz CH_2-2a), 1.91 (1H, dd, J=7.5, 7.6 Hz, CH_2-2b), 1.28 (2H, m CH2-15), 0.98 (1H, m, CH-16), 0.77, 0.72 (6H, 2d, J=6.3 Hz, CH_3-17,18)

$delta_C$ (250 MHz, DMSO) 173.3, 170.9, 167.6, 167.2, 155.7, 130.5, 129.6, 113.6, 66.7, 53.7, 40.4-36.0,

35.7, 35.2, 25.1, 24.9, 24.6, 22.8, 21.4

Example 3

4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxymethyl)-phenylalanine-N-methylamide

Example 3a

4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxymethyl)-phenylalanine-N-methylamide

[4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-carboxylic acid) phenylalanine-N-methylamide (from example 2a, 0.5g, 1.08 mmol) was dissolved in CH_2Cl_2 (20 ml) and cooled to 0°C. A solution of diazomethane in ether (3 ml) was added via a pipette until gas evolution ceased and the reaction solution remained a pale yellow colour. After 30 minutes the reaction mixture was treated with 10% acetic acid/ether until the solution was colourless and washed with brine (30 ml). The CH_2Cl_2 layer was dried and the solvent removed under reduced pressure to give the title compound as a white solid (0.45g, 87%).

$C_{25}H_{33}N_2O_7$ MWt = 478.69

$delta_H$ (250 MHz, $CDCl_3$) 7.16 (2H, d, J=8.6 Hz, CH-9, 11), 6.83 (2H, d, J=8.6 Hz, CH-8,12), 6.35 (1H, d, J=8.0 Hz, CONH), 5.91 (1H, m, CONHMe), 4.61 (2H, s, CH2-19), 4.49 (1H, q, J=7.9 Hz, CH-5), 3.61 (3H, s, CH3-21), 3.06 (1H, dd, J=6.2 Hz, CH2-6a), 2.96, (1H,

dd, J=9.9 Hz, CH2-6b), 2.71 (3H, d, J=4.8 Hz, CH_3-13), 2.59 (1H, m, CH-3), 2.48 (2H, m, CH_2-2a,2b), 1.53 (2H, m, CH_2-15), 1.44 (9H, s, CH_3-23,24,25), 1.25 (1H, m, CH-16), 0.86 (6H, 2d, J=6.4 Hz, CH_3-17,18).

Example 3b

4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxymethyl) phenylalanine-N-methylamide

The title compound was prepared from 4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-carboxymethyl) phenylalanine-N-methylamide utilising the method described in examples 1i and 1k.

mpt = 187°C

Analysis calculated for $C_{21}H_{31}N_3O_7$ MWt = 437.5

Requires C 57.65 H 7.14 N 9.60

Found C 57.63 N 7.11 N 9.27

$delta_H$ (250 MHz, DMSO) 10.40 (1H, s, CONHOH), 8.76 (1H, s, CONHOH), 7.99 (1H, d, J=8.0 Hz, CONH), 7.86 (1H, m, CONHMe), 7.12 (2H, d, J=8.4 Hz, CH-9,11), 6.81 (2H, d, J=8.4 Hz, CH-8,12), 4.73 (2H, s, CH_2-19), 4.33 (1H, m, CH-5), 3.69 (3H, s, CH_3-21), 2.97 (1H, dd, J=4.6 Hz, CH_2-6a), 2.76 (1H, dd, J=9.9, 10.1 Hz, CH_2-6b) 2.57, 3H, d, J=4.2 Hz, CH_3-13), 2.62-2.56 (1H, m, CH-3), 2.07 (1H, dd, J=6.9, 6.8 Hz, CH_2-2a), 1.93 (1H, dd, J=7.4, 7.6 Hz, CH_2-2b), 1.29 (2H, m, CH_2-15), 1.03 (1H, m, CH-16), 0.78, 0.74 (6H, 2d, J=6.2 Hz, CH_3-17,18).

delta$_C$ (250 MHz, DMSO) 173.3, 170.9, 166.6, 167.2, 155.6, 130.5, 129.6, 113.6, 64.2, 53.7, 51.3, 40.3-38.1, 35.8, 35.1,25.1, 24.6, 22.7, 21.4

Example 4

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-N-benzylamide)-phenylalanine-N-methyl-amide

Example 4a

[4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-N-benzylamide)-phenylalanine-N-methyl-amide.

Utilising the procedure described in example 2b employing benzylamine (0.25g, 2.4 mmol) in lieu of methylamine yielded the title compound as a white solid (0.53g, 81%).

$C_{29}H_{41}N_3O_6$ MWt=527

delta$_H$ (250 MHz, $CDCl_3$ 7.40-7.27 (5H, m, CH-23 to 27), 7.17 (2H, d, J=8.6 Hz, CH-9,11), 6.92 (1H, m, CONHBz), 6.85 (2H, d, J=8.6 Hz, CH-8,12), 6.29 (1H, d, J=7.8 Hz, CONH), 5.96 (1H, m, CONHMe), 4.56-4.45 (5H, m, CH-5, CH_2-21, CH_2-19), 3.04 (2H, m, CH_2-6), 2.70 (3H, d, J=4.8 Hz, CH_3-13), 2.58 (1H, m, CH-3), 2.43 (1H, dd, J=8.5 Hz, CH_2-2a), 2.33 (1H, dd, J=5.3 Hz, CH_2-2b), 1.45 (2H, m, CH_2-15), 1.41 (9H, s, CH_3-23,24,25), 1.20

(1H, m, CH-16), 0.86 (6H, 2d, J=6.3, 6.2 Hz, CH_3-17,18).

Example 4b

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-N-benzylamide)-phenylalanine-N-methylamide

The title compound was prepared from [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethylene-carboxy-N-benzylamide) phenylalanine-N-methylamide utilising the method described in examples 1i to 1k.

mpt= 206°C

Analysis calculated for $C_{27}H_{36}N_4O_6$ MWt = 512.6

Requires C 63.26 H 7.08 N 10.93

Found C 62.52 H 7.09 N 10.97

$delta_H$ (250 MHz, DMSO) 10.41 (1H, s, CONHOH), 8.76 (1H, s, CONHOH), 8.62 (1H, t, J=6.1 Hz, CONHCHPh), 8.01 (1H, d, J=8.3 Hz, CONH), 7.87 (1H, m, CONHMe), 7.26 (5H, m, CH-23 to 27), 7.13 (2H, d, J=8.5 Hz, CH-9,11), 6.86 (2H, d, J=8.5 Hz, CH-8,12), 4.48 (2H, s, CH_2-19), 4.34 (2H, d, J=6.0 Hz, CH_2-21), 2.97 (1H, dd, J=4.5, 4.8 Hz, CH_2-6a), 2.76 (1H, dd, J=9.5, 9.6 Hz, CH_2-6b), 2.64-2.55 (1H, bm, CH-3), 2.56 (3H, d, J=4.4 Hz, CH_3-13) 2.06 (1H, dd, J=3.2, 7.1 Hz, CH_2-2a), 1.92 (1H,

dd, J=7.6 Hz, CH_2-2b), 1.28 (2H, m, CH_2-15), 0.97 (1H, m, CH-16), 0.78, 0.73 (6H, 2d, J=6.3 Hz, CH_3-17,18).

$delta_C$ (250 MHz, DMSO) 173.5, 170.9, 167.3, 167.2, 155.7, 138.6, 130.5, 129.6, 127.8, 126.8, 126.3, 113.9, 66.6, 53.7, 41.32, 40.1-38.1, 35.2, 25.1, 24.7, 22.8, 21.4

Example 5

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-beta-alanine)phenylalanine-N-methylamide

Example 5a

[4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-carboxy-beta-alanine benzyl ester) phenylalanine-N-methylamide

Utilising the procedure described in example 2b employing beta-alanine benzyl ester (0.76g, 2.16 mmol) in lieu of methylamine yielded the title compound as a yellow oil (0.65g, 97%).

$C_{34}H_{47}N_3O_8$ MWt = 625

$delta_H$ (250 MHz, $CDCl_3$) 7.35 (5H, s, CH-26 to 30), 7.17 (2H, d, J=8.5 Hz, CH-9,11), 7.19 (1H, m, CONHCH$_2$), 6.82 (2H,d, J=8.5 Hz, CH-8,12), 6.33 (1H, d, J=7.8 Hz, CONH), 6.01 (1H, m, CONHMe), 5.13 (2H, s, CH_2-24), 4.49 (1H, q, J=6.7, 7.6 Hz, CH-5), 4.44 (2H, s, CH_2-19),

3.64 (2H, q, J=6.1 Hz, CH_2-21), 3.06 (2H, m, CH_2-6a, 6b), 2.72 (3H, d, J=4.8 Hz, CH_3-13), 2.66-2.62 (3H, m, CH2-22, CH-3), 2.50-2.39 (2H, m, $CH_2$2a,b), 1.48 (2H, m, CH_2-15), 1.22, (1H, m, CH-16). 0.87, 0.84 (6H, 2d, J=6.4, 6.3 Hz, CH_3-17, 18).

Example 5b

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-beta-alanine)phenylalanine-N-methylamide

The title compound was prepared from [4-(t-butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxy-beta-alanine benzyl ester)phenyl alanine-N-methylamide utilising the method described in examples 1i to 1k.

mpt = 195°C

Analysis calculated for $C_{23}H_{34}N_4O_8$ MWt = 494.6

Requires C 55.86 H 6.93 N 11.33

Found C 55.94 H 6.96 N 11.51

$delta_H$ (250 MHz, MeOD) 7.13 (2H, d, J=8.5 Hz, CH-9,11), 6.86 (2H, d, J=8.5 Hz, CH-8,12), 4.47-4.42 (1H, m, CH-5), 4.42 (2H, s, CH_2-19), 3.48 (2H, t, J=6.7 Hz, CH_2-21), 3.06 (1H, dd, J=6.4, 6.3 Hz, CH_2-6a), 2.85 (1H, dd, J=8.7, 8.8 Hz, CH_2-6b), 2.80-2.64 (1H, m, CH-3), 2.64 (3H, s, CH_3-13), 2.50 (2H, t, J=6.7 Hz, CH_2-22), 2.17 (1H, dd, J=6.5 Hz, CH_2-2a), 2.04 (1H, dd, J=6.5 Hz, CH_2-2b) 1.36 (2H, m, CH_2-15), 1.06 (1H, m,

CH-16), 0.81, 0.77 (6H, 2d, J=6.3 Hz, CH_3-17,18).

$delta_C$ (250 MHz, MeOD) 177.0, 175.5, 173.9, 171.1, 170.6, 157.9, 132.0, 131.4, 115.8, 68.3, 56.2, 50.0, 49.6-47.9, 42.5, 42.4, 37.9, 36.8, 36.0, 34.6, 26.8, 26.3, 23.5, 22.

Example 6

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxy-glycine methyl ester) phenylalanine-N-methylamide

Example 6a

[4-(t-Butoxy)-2R-isobutylsuccinyl]-L-4-oxymethyl carboxy-glycine methylester)-phenylalanine-N-methylamide.

Utilising the procedure described in example 2b employing glycine methyl ester hydrochloride (0.13g, 1.07 mmol) in lieu of methylamine yielded the title compound as a white solid (0.45g, 78.5%).

$C_{27}H_{41}N_8O_8$ MWt = 535.64

$delta_H$ (250 MHz, $CDCl_3$) 7.17 (2H, d, J=8.6 Hz, CH-9,11), 7.15 (1H, m, $CH_2CONHCH_2$), 6.83 (2H, d, J=8.6 Hz, CH-8), 6.45 (1H, d, J=8.0 Hz, CHCONHCH), 6.26 (1H, m, CONHMe), 4.53 (1H, m, CH-5), 4.48 (2H, s, CH_2-19), 4.13 (2H, d, J=6.3 Hz, CH_2-21), 3.76 (3H, s, CH_3-23), 3.04 (2H, m, CH_2-6), 2.72 (3H, d, J=4.8 Hz, CH_3-13),

2.51 (1H, m, CH-3), 2.42 (2H, m. CH_2-2), 1.47 (2H, m, CH_2-15), 1.43 (9H, s, CH_3-24,25,26), 1.19 (1H, m, CH-16), 0.83 (6H, dd, J=6.3 Hz, CH3-17,18).

Example 6b

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxy-glycinemethylester)-phenylalanine-N-methylamide

The title compound was prepared from [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-4-oxymethyl carboxy-glycine methyl ester)-phenylalanine-N-methylamide utilising the method described in examples 1i to 1k.

mpt = 180-185°C

Analysis calculated for $C_{23}H_{34}N_4O_8$ MWt = 494.55

Requires C 55.86 H 6.93 N 11.33

Found C 53.45 H 6.83 N 11.50

$delta_H$ (250 MHz, MeOD) 7.14 (2H, d, J 8.6 Hz, CH-9,11)6.89, (2H, d, J=8.6 Hz, CH-8,12), 4.49 (2H,s, CH_2-19), 4.44 (1H, m, CH-5), 3.99 (2H, s, CH_2-21), 3.69 (3H, s, CH_3-23), 3.11-2.81 (2H, m, CH_2-6), 2.72-2.63 (1H, m, CH-3), 2.64 (3H, s, CH_3-13), 2.21 (1H,dd, J=7.8 Hz, CH_2-2a), 2.04 (1H, dd, J=6.7,6.6 Hz, CH_2-2b), 1.35 (2H, m, CH_2-15) 1.05 (1H, m, CH-16), 0.79 (6H, dd, J=6.4 Hz, CH_3-17,18).

$delta_C$ (250 MHz, MeOD) 177.1, 173.9, 171.8, 171.6,

170.6, 158.0, 132.1, 131.4, 115.9, 68.3, 56.3, 52.7, 50.0-48.0, 42.6, 42.4, 41.5, 37.9, 36.8, 26.8, 26.3, 22.3

Example 7

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxyethyl)-phenylalanine-N-methylamide.

Example 7a

[4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxyethyl)-phenylalanine-N-methylamide.

When the procedure described in example 1g was utilised employing [4-(t-butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxybenzyl ester) phenylalanine-N-methylamide (from example 1h 9.10g, 16.41 mmol) in lieu of [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-benzyloxy) phenylalanine-N-methylamide a transesterification reaction occurred and an ethyl group was transferred from the solvent to the reactant molecule. The reaction yielded after chromatography (flash silica, 100% ethyl acetate) the title compound as a white solid (0.51g, 6.3%)

$C_{26}H_{46}N_2O_7$ MWt = 492.62

^{1}Hnmr delta$_H$ (250 MHz, $CDCl_3$) 7.09 (2H, d, J=8.6 Hz, CH-9,11), 6.77 (2H, d, J=8.6 Hz, CH-8,12), 6.68 (1H, d, J=8.8 Hz, CONHCH), 6.57 (1H, m, CONHMe), 4.55 (1H, m, CH-5), 4.53 (2H, s, CH_2-19), 4.21 (2H, q, J=7.1 Hz, CH_2-21), 2.97 (2H, m, CH_2-6), 2.72-2.52 (1H, m, CH-3),

2.65 (3H, d, J=4.8 Hz, CH_3-13), 2.43 (1H, dd, J=7.8 Hz, CH_2-2a), 2.27 (1H, dd, J=6.8 Hz, CH_2-2b), 1.42 (2H, m, CH_2-15), 1.37 (9H, s, CH_3-23,24,25), 1.25 (3H, t, J=7.1 Hz, CH_3-22), 1.14 (1H, m, CH-16), 0.78 (6H, dd, J=6.4 Hz, CH_3-17,18).

Example 7b

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxyethyl)-phenylalanine-N-methylamide.

The title compound was prepared from [4-(t-butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-carboxyethyl)-phenylalanine-N-methylamide utilising the method described in examples 1i to 1k.

mpt 185°C

Analysis calculated for $C_{22}H_{33}N_3O_7$ MWt = 451.52

Requires C 58.52 H 7.37 N 9.31

Found C 58.54 H 7.28 N 9.26

$delta_H$ (250 MHz, MeOD) 7.11 (2H, d, J=8.6 Hz, CH-9,11), 6.79 (2H,d, J=8.6 Hz, CH-8,12), 4.61 (2H, s, CH_2-19), 4.43 (1H, m, CH-5), 4.19 (2H, q, J=7.1, 7.2 Hz,CH_2-21), 3.05 (1H, dd, J=6.4, 6.4 Hz, CH_2-6a), 2.81 (1H, dd, J=9.1, 8.9 Hz, CH_2-6b), 2.64 (3H, s, CH_3-13), 2.78-2.58 (1H, m, CH-3), 2.12 (1H, dd, J=7.8, 7.9 Hz, CH_2-2a), 2.06 (1H, dd, J=6.7, 6.8 Hz, CH_2-2b), 1.31 (2H,m, CH_2-15), 1.24 (3H, t, J=7.1 Hz, CH_3-22) 1.09 (1H, m, CH-16), 0.79 (6H, dd, J=6.4 Hz, CH_3-17, 18).

delta$_C$ (250 MHz, MeOD) 177.2, 174.0, 171.0, 170.6, 158.1, 131.8, 131.2, 115.6, 66.4, 62.4, 56.4, 50.1,-48.0, 42.6, 42.4, 38.1, 36.9, 26.8, 26.4, 23.6, 22.4, 14.

Example 8

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxyglycine)phenylalanine-N-methylamide

Example 8a

[4-(t-Butoxycarbonyl)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxyglycine benzyl ester)-phenylalanine-N-methylamide

Utilising the procedure described in example 2b employing glycine benzyl ester hydrochloride (0.24g, 1.21 mmol) in lieu of methylamine yielded the title compound as a white solid (0.55g, 89.5%).

$C_{33}H_{45}N_3O_8$ MWt = 611.74

delta$_H$ (250 MHz, $CDCl_3$) 7.38 (5H, m, CH-24 to 29), 7.22-7.11 (1H, m, CONHCH$_2$CO$_2$Bz), 7.17 (2H, d, J=7.76 Hz, CH-9, 11), 6.84 (2H, d, J=7.6 Hz, CH-8, 12), 6.47 (1H, d, J=8.1 Hz, CHCONHCH), 6.24 (1H, m, CONHMe), 5.19 (2H, s, CH_2-23), 4.62-4.42 (1H, m,CH-5), 4.48 (2H, s, CH_2-19), 4.16 (2H, d, J=6.5 Hz, CH_2-21), 3.05 (2H, m, CH_2-6), 2.77-2.55 (1H, m, CH-3), 2.73 (3H, d, J=4.2 Hz, CH_3-13), 2.53 (1H, dd, J=6.6 Hz, CH_2-2a), 2.35 (1H, dd, J=5.3 Hz, CH_2-2b), 1.55-1.37 (2H, m, CH_2-15), 1.45 (9H, s, CH_3-30,31,32), 1.22, (1H, m, CH-16), 0.97 (6H,

m, CH_3-17,18).

Example 8b

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxyglycine)phenylalanine-N-methylamide

The title compound was prepared from [4-(t-butoxycarbonyl)-2R-isobutylsuccinyl]-L-(4-oxymethyl-carboxyglycine benzyl ester)-phenylalanine-N-methylamide utilising the method described in examples 1i to 1k.

mpt = 142.5°C

Analysis calculated for $C_{22}H_{32}N_4O_8$ MWt = 480.52

Requires C 54.99; H 6.71 N 11.66

Found C 54.19; H 6.87 N 10.96

$delta_H$ (250 MHz, DMSO) 10.42 (1H, s, CONHOH), 8.32 (1H, m, $CONHCH_2CO_2H$), 8.01 (1H, d, J=8.1 Hz, CHCONHCH), 7.87 (1H, m, CONHMe), 7.13 (2H, d, J=7.6Hz, CH-9,11), 6.87 (2H, d, J=7.3 Hz, CH-8,12), 4.46 (2H, s, CH_2-21), 4.33 (1H, m, CH-5), 3.80 (2H, d, J=5.5 Hz, CH_2-19), 2.96 (1H, dd, J=4.6, 4.5 Hz, CH_2-6a), 2.75 (1H, m, CH_2-6b), 2.56 (3H, s, CH_3-13), 2.68-2.43 (1H, m, CH-3), 2.05 (1H, dd, J=7.0, 6.6 Hz, CH_2-2a), 1.91 (1H, dd, J=5.3 Hz, CH_2-2b), 1.26 (2H, m, CH_2-15), 1.05 (1H, m, CH-16), 0.75 (6H, dd, J=5.7 Hz, CH_3-17,18).

$delta_C$ (250 MHz, DMSO) 173.4, 170.9, 170.5, 167.6,

167.2, 155.6, 130.6, 129.6, 113.9, 66.5, 53.7, 40.3, 40.2, 39.7-38.4, 5.9, 35.2, 25.9, 25.1, 22.8, 21.4

Example 9

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxy-N,N-dimethylamide)-phenylalanine-N-methylamide

Example 9a

[4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxy-N,N-dimethylamide)-phenylalanine-N-methylamide.

Utilising the procedure described in example 2b employing dimethylamine hydrochloride (0.11g, 1.30 mmol) in lieu of methylamine yielded the title compound as a white solid (0.49g, 92.3%).

$C_{26}H_{41}N_3O_6$ MWt = 491.63

$delta_H$ (250 MHz, $CDCl_3$) 7.13 (2H, d, J=8.5 Hz, CH-9,11), 6.85 (2H, d, J=8.5 Hz, CH-8,12), 6.42 (1H, d, J=8.0 Hz, CHCONHCH), 6.19 (1H, m, CONHMe), 4.63 (2H, s, CH_2-19), 4.50 (1H, m, CH-5), 3.12-2.82 (2H, m, CH_2-6), 3.07 (3H, s, CH_3-21), 2.96 (3H, s, CH_3-22), 2.68 (3H, d, J=4.5 Hz, CH_3-13), 2.62 (1H, m, CH-3), 2.52 (1H, dd, J=8.5 Hz, CH_2-2a), 2.33 (1H, dd, J=4.5 Hz, CH_2-2b), 1.55-1.35 (2H, m, CH_2-15), 1.42 (9H, s, CH_3-23,24,25), 1.19 (1H, m, CH-16), 0.83 (6H, dd, J=6.3 Hz, CH_3-17,18).

Example 9b

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxy-N,N-dimethylamide)-phenylalanine-N-methylamide

The title compound was prepared from [4-(t-Butoxy)-2R-isobutylsuccinyl]-L-(4-oxymethyl-carboxy-N,N-dimethylamide)-phenylalanine-N-methylamide utilising the method described in examples 1i to 1k.

mpt 197°C

Analysis calculated for $C_{22}H_{34}N_4O_6$ MWt = 450.54

Requires C 58.65 H 7.61 N 12.44

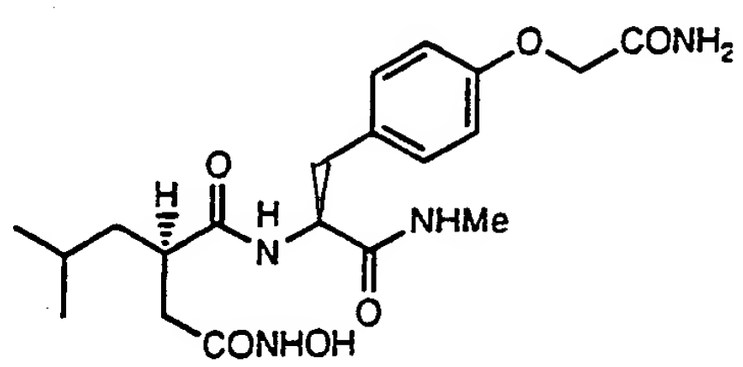
Found C 58.58 H 7.54 N 12.33

$delta_H$ (150 MHz, DMSO) 0.42 (1H, s, CONHOH), 8.77 (1H, s, CONHOH), 7.99 (1H, d, J=8.0 Hz, CHCONHCH), 7.87 (1H, m, CONHMe), 7.09 (2H, d, J=8.5 Hz, CH-9,11), 6.78 (2H, d, J=8.5Hz, CH-8,12), 4.71 (2H, s, CH_2-19), 4.32 (1H, m, CH-5), 2.98 (3H, s, CH_3-21), 2.94 (1H, m, CH_2-6a), 2.83 (3H, s, CH_3-22), 2.73 (1H, m, CH_2-6b), 2.55 (3H, m, CH_3-13), 2.68-2.45 (1H, m, CH-3), 2.01 (1H, dd, J=6.8 Hz, CH_2-2a), 1.91 (1H, dd, J=6.8 Hz, CH_2-2b), 1.28 (2H, m, CH_2-15), 0.99 (1H, m, CH-16), 0.74 (6H, dd, J=6.3, 6.2 Hz, CH_3-17,18).

$delta_C$ (250 MHz, $CDCl_3$) 173.4, 170.9, 167.2, 166.8, 156.1, 130.0, 129.4, 113.7, 65.5, 53.7, 40.9-38.0, 35.9, 35.2, 34.5, 25.1, 24.6, 21.4

Example 10

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxamide)-phenylalanine-N-methylamide (BB 802)



a) [4-t-Butoxy-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxamide)-phenylalanine-N-methylamide.

[4-t-Butoxy-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxylic acid)-phenylalanine-N-methylamide (see example 2a, 1.10g, 2.36 mmol) was dissolved in DMF (10ml) and cooled to 0°. Pentafluorophenol (0.87g, 4.72 mmol), aqueous ammonia (35%, 0.14g, 2.83 mmol), N-methyl morpholine (0.29g, 2.83 mmol) and WSCDI (0.54g, 2.83 mmol) were added and the reaction stirred overnight. The solvent was removed under high vacuum to leave a yellow oil which was dissolved in DCM and washed sequentially with saturated sodium carbonate, 2M hydrochloric acid and brine. The organic layer was dried over magnesium sulphate, filtered then the sovent removed to leave a white soild (0.89g, 1.92 mmol, 81%): ^{1}H-NMR; δ ($CDCl_3$), 7.17 (2H, d, J=8.6 Hz, Aryl-H), 6.83 (2H, d, J=8.6 Hz, Aryl-H), 6.57 (2H, bs, CON$\underline{H}_2$), 6.29 (1H, bq, N$\underline{H}$Me), 6.17 (1H, bs, CON$\underline{H}$CH), 4.57 (1H, q, J=7.0 Hz, COC$\underline{H}$NH), 4.44 (2H, s, OC$\underline{H}_2$CO), 3.04 (2H, d, J=7.0 Hz, CHC$\underline{H}_2$Ar), 2.71 (3H, d, J=4.8 Hz, NHC$\underline{H}_3$), 2.60 (1H, m, iBuC$\underline{H}$), 2.50 (1H, dd, J= 14, 9 Hz, C$\underline{H}_2$CONHOH), 2.33 (1H, dd, J=14, 5 Hz, C$\underline{H}_2$CONHOH), 1.43 (11H, m + s, $(CH_3)_2C\underline{H}C\underline{H}_2$ and $(C\underline{H}_3)_3CO$), 1.17 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 0.86 (3H, d, J=6.4 Hz, $CH(C\underline{H}_3)_2$), and 0.83 (3H, d, J=6.3 Hz, $CH(C\underline{H}_3)_2$).

b) [4-(N-Benzylamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxamide)-phenylalanine-N-methylamide

[4-t-Butoxy-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxamide)-phenylalanine-N-methylamide (0.88g, 1.90 mmol) was taken up in

trifluoroacetic acid/water (95/5) and stored at 4° overnight. The trifluoroacetic acid was removed by evaporation and the residue taken up in DCM and washed with 2M sodium carbonate solution. The precipitated product was filtered off and dried to give the acid (0.57g, 1.40 mmol) as a white solid.

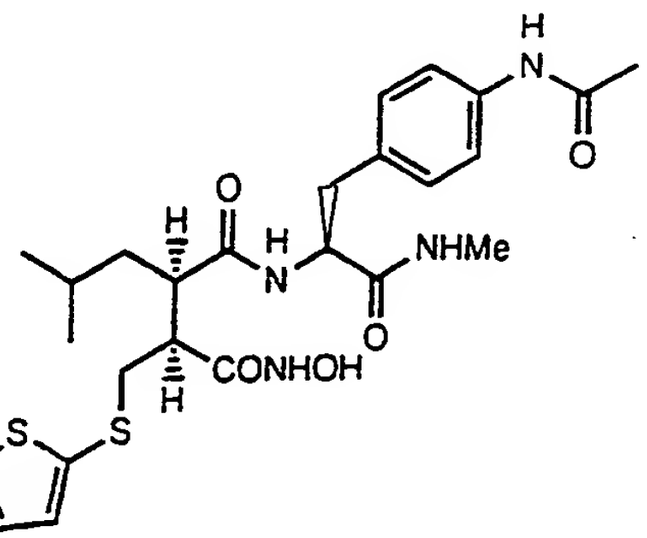
The acid from above (0.57g, 1.40 mmol) was dissolved in the minimum quantitiy of DMF. Pentafluorophenol (0.52g, 2.80 mmol), O-benzylhydroxylamine (0.34g, 2.80 mmol), N-methylmorpholine (0.18g, 1.82 mmol) and WSCDI (0.35g, 1.82 mmol) were added and the mixture stirred at room temperature overnight. The precipitated product was collected by filtration and washed with cold DCM, giving the title compound as a white solid (0.35g, 0.68 mmol, 49%): ^{1}H-NMR; δ (DMSO-d_6), 11.05 (1H, s, NHOH), 8.04 (1H, bd. J=8 Hz, CONHCH), 7.86 (1H, bm, NHMe), 7.5 - 7.3 (7H, s + m, $CONH_2$ + Ph), 7.12 (2H, d, J=8.6 Hz, Aryl-H), 6.82 (2H, d, J=8.6 Hz, Aryl-H), 4.75 (2H, s, OCH_2Ph), 4.33 (3H, bs, COCHNH and OCH_2CO), 2.93 (1H, dd, J=14, 5 Hz, $CHCH_2Ar$), 2.79 (1H, dd, J=14,10 Hz, $CHCH_2Ar$), 2.60 (1H, m, ^{i}BuCH), 2.55 (3H, d, J=4.8 Hz, $NHCH_3$), 2.08 (1H, dd, J= 14, 7 Hz, $CH_2CONHOH$), 1.94 (1H, dd, J=14, 7 Hz, $CH_2CONHOH$), 1.25 (2H, m, $(CH_3)_2CHCH_2$), 0.95 (1H, m, $(CH_3)_2CHCH_2$), 0.78 (3H, d, J=6.4 Hz. $CH(CH_3)_2$), and 0.73 (3H, d, J=6.3 Hz, $CH(CH_3)_2$).

c) [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxamide)- phenylalanine-N-methylamide.

[4-(N-Benzylamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxamide)-phenylalanine-N-methylamide (0.34g, 0.66 mmol) was dissolved in 10% cyclohexene/ethanol, 10% palladium on charcoal (40mg) added and the mixture heated at reflux for 1 hour. The reaction mixture was filtered hot then the solvents removed to leave the product as a white solid: m.p. 206.0 - 206.0°; ^{1}H-NMR; δ (Methanol-d_4), 7.13 (2H, J =8.6 Hz, aryl-H), 6.86 (2H, d, J =8.6 Hz, aryl-H), 4.51-4.38 (1H, m, NCHCO), 4.41 (2H, s, $COCH_2CONH_2$), 3.06 (1H, dd, J =6.4 Hz, $CHCH_2Ph$), 2.84 (1H, dd, J=8.9 Hz, $CHCH_2Ph$), 2.71-2.57 (1H, m, ^{i}BuCH), 2.68 (3H, s, $CONHCH_3$), 2.14 (1H, dd, J= 8, 10 Hz, $CHCH_2CONHOH$), 2.04 (1H, dd, J=6, 7 Hz, $CHCH_2CONHOH$), 1.36 (2H, m, $(CH_3)_2CHCH_2CH$), 1.07(1H, m, $(CH_3)_2CHCH_2CH$), and 0.79 (6H, 2d, J =6.4 Hz, $CH(CH_3)_2$).; ^{13}C NMR: δ (Methanol-d_4) 177.0, 174.1, 173.9, 170.6, 158.0, 132.0, 131.4, 115.7, 68.0, 57.1, 42.6, 42.4, 37.8, 36.8, 26.3, 25.7, 23.5 and 22.3.

Example 11

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-acetylamino)-phenylalanine-N-methylamide (BB 887)



a) 4-Aminophenylalanine methyl ester.

4-Aminophenylalanine (20.0g, 96.4 mmol) was taken up in methanol (400 mL), cooled to -10° and thionyl chloride (100 mL) added dropwise maintaining the temperature of the reaction mixture below 0°. The solution was warmed to room temperature then refluxed for 24 hours. The solvent was removed to give a crude wax which was dissolved in ethyl acetate (500 mL) and washed with 1M sodium carbonate (100 mL). The aqueous layer was re-extracted with ethyl acetate (6 X 200 mL) and the combined organic layers dried over magnesium sulphate. Solvent removal gave the product as a pale yellow solid (16.6g, 85.2 mmol, 88%): ^{1}H-NMR; δ ($CDCl_3$), 6.93 (2H, d, J=8.3 Hz, Aryl-H), 6.61 (2H, d, J=8.3 Hz, Aryl-H), 3.70 (3H, s, OCH_3), 3.66 (1H, dd, J=5.2, 7.8 Hz, NC<u>H</u>CO), 2.96 (1H, dd, J=13.6, 5.2 Hz, C<u>H$_2$</u>Ar), and 2.75 (1H, dd, J=13.6, 7.7 Hz, C<u>H$_2$</u>Ar).

b) 4-Aminophenylalanine-N-methylamide.

4-Aminophenylalanine methyl ester (16.5g, 85 mmol) was taken up in ethanol (200 mL) and stirred at 0°. Methylamine (100 mL, 8.03M in ethanol) was added dropwise and the mixture stirred at room temperature for four days. Solvent was removed at reduced pressure to leave the title compound as a yellow solid (16.4g, 100%): ^{1}H-NMR; δ ($CDCl_3$), 7.24 (1H, bs, CON<u>H</u>), 6.95 (2H, d, J=8.3 Hz, Aryl-H), 6.60 (2H, d, J=8.3 Hz, Aryl-H), 3.49 (1H, dd, J=4.1, 9.2 Hz, NC<u>H</u>CO), 3.09 (1H, dd, J=13.8, 4.1 Hz, C<u>H$_2$</u>Ar), 2.77

(3H. d. J=5.0 Hz, NHC$\underline{H}_3$), and 2.55 (1H, dd, J=13.8, 9.2 Hz, C$\underline{H}_2$Ar).

c) [4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-aminophenylalanine-N-methylamide.

4-Aminophenylalanine-N-methylamide (4.92g, 25.5 mmol) was taken up in DMF (50 mL) and stirred at 0°, benzyl (2-benzyloxycarbonyl-5-methyl-3R-pentafluorophenoxycarbonyl)-hexanoate (11.10g, 28 mmol) was added and the mixture stirred at room temperature for six hours then overnight at 4°. The crude reaction mixture was taken up in diethyl ether then washed twice with 1M sodium carbonate, dried over magnesium sulphate. Solvent removal under vacuum left the crude product as a yellow foam which was purified from unreacted starting ester by column chromatography (silica gel, 0 - 3% methanol/DCM) to give the title compound as a foam (11.03g, 19.2 mmol, 76%) containing a mixture of diastereomers: ^{1}H-NMR; δ ($CDCl_3$), 7.30 (10H, m, Ph), 6.98 (2H, d, J=8.3Hz, Aryl-H), 6.59 (2H, d, J=8, 3 Hz, Aryl-H), 5.68 (1H, m, N$\underline{H}$Me), 5.12 (4H, m, C$\underline{H}_2$Ph), 4.42 (1H, m, NC$\underline{H}$CO), 3.82 (1H, d, J=9.3 Hz, C$\underline{H}$(CO_2Bn)$_2$), 3.60 (1H, s, NH_2), 2.95 (3H, m, C$\underline{H}_2$Ar and ^{i}BuC$\underline{H}$), 2.64 (3H, d, J=5.0 Hz, NHC$\underline{H}_3$), 1.56 (1H, m, $(CH_3)_2$CHC$\underline{H}_2$), 1.38 (1H, m, $(CH_3)_2$C$\underline{H}$CH$_2$), 1.02 (1H, m, Me_2CHC$\underline{H}_2$), and 0.78 (6H, m, CH(C$\underline{H}_3$)$_2$).

d) [4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-(N-acetylamino)-phenylalanine-N-methylamide.

[4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-aminophenylalanine-N-methylamide (11.0g, 19.2 mmol) was dissolved in DCM and cooled to 0° then acetic anhydride (2.16g, 21.2 mmol), DMAP (50mg) and triethylamine (2.14g, 21.2 mmol) added. The reaction mixture was stirred for 2 hours then the reaction mixture diluted with an equivalent volume of DCM and washed twice with 2M hydrochloric acid then with brine and dried over magnesium sulphate. Filtration and sovent removal gave a pale yellow solid which was recrystallised from ethyl acetate/hexane (7.69g, 12.5 mmol, 65%): ^{1}H-NMR; δ ($CDCl_3$), 7.59 (1H, s, ArN$\underline{H}$CO), 7.42 (2H, d, J=8.4 Hz, Aryl-H), 7.30 (10H, m, Ph), 7.13 (2H, d, J=8.4 Hz, Aryl-H), 6.68 (1H, d, J=7.9 Hz, CHN$\underline{H}$CO), 6.00 (1H, m, N$\underline{H}$Me), 5.09 (4H, m, C$\underline{H}_2$Ph), 4.50 (1H, m, NC$\underline{H}$CO), 3.79 (1H, d, J=9.3 Hz, C$\underline{H}$(CO_2Bn)$_2$), 2.99 (3H, m, C$\underline{H}_2$Ar and ^{i}BuC$\underline{H}$), 2.65 (3H, d, J=5.0 Hz, NHC$\underline{H}_3$), 2.13 (3H, s, COC$\underline{H}_3$), 1.55 (1H, m, Me_2CHC$\underline{H}_2$), 1.35 (1H, m, Me_2C$\underline{H}$CH$_2$), 1.06 (1H, m, Me_2CHC$\underline{H}_2$), 0.77 (3H, d, J=6 Hz, CH(C$\underline{H}_3$)$_2$ and 0.74 (3H, d, J=6 Hz, CH(C$\underline{H}_3$)$_2$).

e) [Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(N-acetylamino)-phenylalanine-N-methylamide.

[4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-(N-acetylamino)-phenylalanine-N-methylamide (7.69g, 12.5 mmol) was dissolved in ethanol (200 mL), 20% palladium on charcoal (1.5g) added and the mixture subjected to an atmosphere of hydrogen for 1 hour. The catalyst was removed by filtration and the sovent removed under vacuum to give the diacid as a foamy white solid (about 6g). This crude diacid was taken up in ethanol (250 mL), piperidine (1.17g, 13.7 mmol) and formaldehyde (37% aqueous solution, 9.4 mL, 125 mmol) were added and the reaction stirred at room temperature for three days. Solvent removal gave a clear oil which was taken up in ethyl acetate and washed twice with 1M hydrochloric acid and then with brine. The organic layer was separated and dried over magnesium sulphate then the solvent removed to give the title compound as a white solid (2.10g, 5.2 mmol, 42%): ^{1}H-NMR; δ (Methanol-d_4), 7.81 (1H, s, ArNHCO), 7.39 (2H, d, J=8.4 Hz, Aryl-H), 7.07 (2H, d, J=8.4 Hz, Aryl-H), 6.19 (1H, s, H_2C=C), 5.59 (1H, s, H_2C=C), 4.47 (1H, m, NCHCO), 3.51 (1H, m, ^{i}BuCH), 2.99 (1H, dd, J=13.8, 6.1 Hz, CH_2Ar), 2.81 (1H, dd, J=13.8, 8.7 Hz, CH_2Ar), 2.64 (3H, s, NHCH_3), 2.06 (3H, s, COCH_3), 1.61 (1H, m, Me_2CHCH_2), 1.37 (1H, m, Me_2CHCH_2), 0.85 (3H, d, J=6 Hz, CH(CH_3)$_2$), and 0.81 (3H, d, J=6 Hz, CH(CH_3)$_2$).

f) [4-Hydroxy-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-acetylamino)-phenylalanine-N-methylamide.

[Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(N-acetylamino)-phenylalanine-N-methylamide (1.63g, 4.04 mmol) was taken up in methanol (20 mL) and thiophene-2-thiol (5g) added then the mixture heated at reflux under argon overnight. The methanol was evaporated to give a crude yellow solid which was washed with cold diethyl ether to remove the bulk of the excess thiol. The title compound was then purified by crystallisation from ethyl acetate (1.61g, 3.1 mmol, 77%): ^{1}H-NMR; δ (Methanol-d_4), 7.52 (2H, d, J=8.4 Hz, Aryl-H), 7.37 (1H, dd, J=5.3, 1.2 Hz, Thienyl-H5), 7.18 (2H, d, J=8.4 Hz, Aryl-H), 6.99 (1H, dd, J=3.4, 1.0 Hz, Thienyl-H3), 6.90 (1H, dd, J=3.5, 5.3 Hz, Thienyl-H4), 4.47 (1H, m, NCHCO), 3.51 (1H, m, ^{i}BuCH), 2.98 (1H, dd, J=13.8, 5.2 Hz, CH_2Ar), 2.78 (1H, dd, J=13.7, 10.4 Hz, CH_2Ar), 2.65 (3H, s, NHCH_3), 2.46 (3H, m, SCH_2CH), 2.06 (3H, s, COCH_3), 1.53 (1H, m, Me_2CHCH_2), 1.40 (1H, m, Me_2CHCH_2), 0.99 (1H, m, Me_2CHCH_2), 0.82 (3H, d, J=6 Hz, CH(CH_3)$_2$), and 0.75 (3H, d, J=6 Hz,

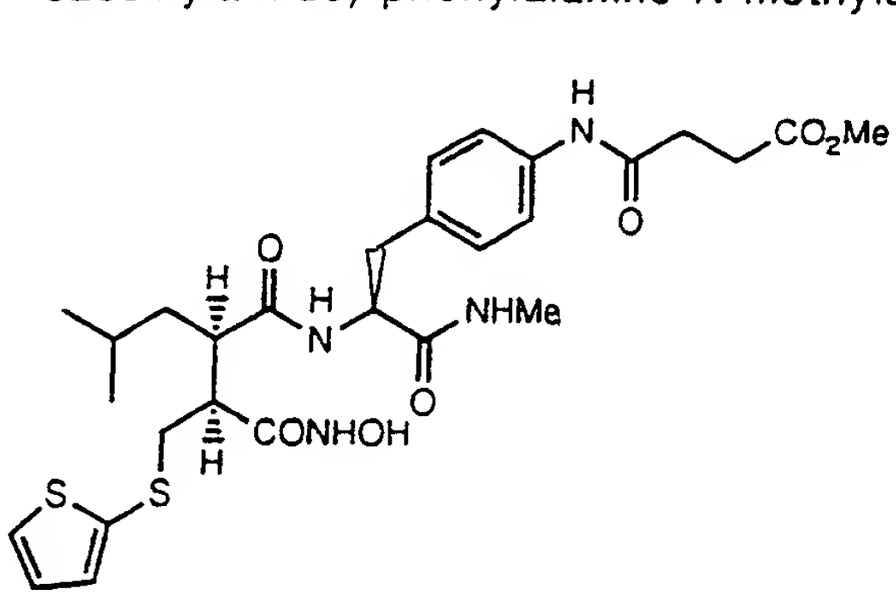
$CH(C\underline{H}_3)_2$).

g) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-acetylamino)-phenylalanine-N-methylamide.

[4-Hydroxy-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-acetylamino)-phenylalanine-N-methylamide (1.08g, 2.08 mmol) was taken up in DMF (20 mL) and cooled to 0° while HOBT (0.36g, 2.70 mmol), NMM (0.27g, 2.70 mmol) and WSCDI (0.52g, 2.70 mmol) were added. The reaction was stirred at 0° for 3 hours then hydroxylamine hydrochloride (0.29g, 4.16 mmol) and NMM (0.42g, 4.20 mmol) were added and the reaction allowed to warm to room temperature overnight. The DMF was removed under reduced pressure and the resultant crude oil was taken up in diethyl ether/water (1:1) and the resulting solid collected by filtration. Impurities were removed by stirring the solid in boiling ethyl acetate to leave the title compound:^{1}H-NMR ; δ (DMSO-d_6), 10.58 (1H, s, CON$\underline{H}$OH), 9.84 (1H, s, CONHO$\underline{H}$), 8.89 (1H, s, N$\underline{H}$COCH$_3$), 8.23 (1H, d, J=8.4 Hz, CON$\underline{H}$CH), 7.80 (1H, m, CON$\underline{H}$CH$_3$), 7.52 (1H, m, Thienyl-H), 7.50 (2H, m, Aryl-H), 7.15 (2H, d, J = 8.4 Hz, Aryl-H), 4.42 (1H, m, NHC$\underline{H}$CO), 3.02 (1H, m, COC$\underline{H}$CH$_2$S), 2.90-2.62 (2H, m, CHC$\underline{H}_2$Ph), 2.54 (3H, d, J=4.7 Hz, CONHC$\underline{H}_3$), 2.40 (1H, m, ^{i}BuC$\underline{H}$), 2.12 (2H, m, CHC$\underline{H}_2$S), 2.02 (3H, s, COC$\underline{H}_3$), 1.32 (2H, m, C$\underline{H}_2$C$\underline{H}$(CH$_3$)$_2$), 0.83 (1H, m, C$\underline{H}_2$CH(CH$_3$)$_2$), and 0.78 (6H, 2xd, J =6.3 Hz, CH(CH$_3$)$_2$): ^{13}C NMR: δ (DMSO-d_6),171.9, 170.9, 167.5, 167.4, 133.1, 132.2, 131.7, 128.9, 128.7, 127.2, 118.0, 54.1, 45.6, 45.5, 41.7, 40.1, 37.9, 35.8, 25.0, 24.6, 23.6 and 21.1.

Example 12

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)-phenylalanine-N-methylamide (BB 1029)



a) [4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-(N-methylsuccinylamido)-phenylalanine-N-methylamide.

[4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-aminophenylalanine-N-methylamide (from example 11, 14.7g, 25.6 mmol) was dissolved in DCM and stirred at O° while triethylamine (2.85g, 28.2 mmol), methyl succinyl chloride (4.24g, 28.2 mmol) and a catalytic amount of DMAP were added. The cooling bath was removed and the reaction stirred at room temperature for 2 hours. The reaction mixture was washed with 1M hydrochloric acid and saturated brine then dried over magnesium sulphate. Filtration and solvent removal gave the product as a cream solid (17.6g, 25.6 mmol, 100%): ^{1}H-NMR; δ ($CDCl_3$), 7.82 (1H, s, ArNHCO), 7.42 (2H, d, J=8.4 Hz, Aryl-H), 7.30 (10H, m, Ph), 7.13 (2H, d, J=8.4 Hz, Aryl-H), 6.66 (1H, d, J=7.8 Hz, CHNHCO), 5.89 (1H, d, J= 4.7 Hz, NHMe), 5.09 (4H, m, CH_2Ph), 4.47 (1H, dd, J= 14.2, 7.7 Hz, NCHCO), 3.80 (1H, d, J=9.3 Hz, CH($CO_2Bn)_2$), 3.69 (3H, s, CO_2CH_3), 2.92 (3H, m, CH_2Ar and ^{i}BuCH), 2.71 (2H, d, J= 5.8 Hz, $COCH_2CH_2$), 2.65 (5H, m, $NHCH_3$ and CH_2CO_2Me), 1.55 (1H, m, $(CH_3)_2CHCH_2$), 1.33 (1H, m, $(CH_3)_2CHCH_2$), 1.02 (1H, m, Me_2CHCH_2), 0.77 (3H, d, J=6 Hz, $CH(CH_3)_2$ and 0.74 (3H, d, J=6 Hz, $CH(CH_3)_2$).

b) [Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(N-methyl succinyl amido)-phenylalanine-N-methylamide.

[4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-(N-methylsuccinylamido)-phenylalanine-N-methylamide (12.80g, 25.2 mmol) was taken up in ethanol (500 mL), 10% palladium on charcoal added (3.5g) and the mixture stirred under hydrogen for 2 1/2 hours. The catalyst was removed by filtration and the solvent evaporated to leave the crude malonic acid which was used without further purification. This crude diacid was taken up in ethanol (500 mL), piperidine (2.36g, 27.8 mmol) and formaldehyde (37% aqueous solution, 22.7 mL, 278 mmol) were added and the reaction stirred at room temperature for three days. Solvent removal gave a clear oil which was taken up in ethyl acetate and washed twice with 1M hydrochloric acid and then with brine. The organic layer was separated and dried over magnesium sulphate then the solvent removed to give the title compound as a white solid which was purified by recrystallisation from ethyl acetate (5.96g, 12.5 mmol, 50%): ^{1}H-NMR; δ (Methanol-d_4), 7.81 (1H, s, ArNHCO), 7.39 (2H, d, J=8.3 Hz, Aryl-H), 7.06

(2H, d, J=8.4 Hz, Aryl-H), 6.19 (1H, s, $\underline{H}_2C$=C), 5.59 (1H, s, $\underline{H}_2C$=C), 4.48 (1H, m, NC$\underline{H}$CO), 3.51 (1H, m, ^{i}BuC$\underline{H}$), 2.98 (1H, dd, J=13.7, 6.1 Hz, C$\underline{H}_2$Ar), 2.80 (1H, dd, J=13.8, 8.7 Hz, C$\underline{H}_2$Ar), 2.63 (7H, bs, NHC$\underline{H}_3$ and C$\underline{H}_2$C$\underline{H}_2$CO$_2$Me), 1.59 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 1.38 (2H, m, $(CH_3)_2CHC\underline{H}_2$), 0.85 (3H, d, J=6 Hz, CH(C$\underline{H}_3$)$_2$), and 0.81 (3H, d, J=6 Hz, CH(C$\underline{H}_3$)$_2$).

c) [4-Hydroxy-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(N-methylsuccinylamido)-phenylalanine-N-methylamide.

[Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(N-methylsuccinyl amido)-phenylalanine-N-methylamide (1.0g, 2.1 mmol) was taken up in methanol (20 mL) and thiophene-2-thiol (4g) added then the mixture stirred at reflux under argon overnight. Solvent removal gave a yellow solid which was washed twice with diethyl ether to leave the title compound as a white solid (0.96g, 1.62 mmol, 78%): ^{1}H-NMR; δ. (Methanol-d_4), 8.37 (1H, d, J= 8.5, CON$\underline{H}$CH), 7.83 (1H, J=5.6 Hz, N$\underline{H}$Me), 7.51 (2H, d, J=8.5 Hz, Aryl-H), 7.37 (1H, dd, J=5.3, 1.0 Hz, Thienyl-H5), 7.17 (2H, d, J=8.5 Hz, Aryl-H), 6.99 (1H, dd, J=3.6, 1.2 Hz, Thienyl-H3), 6.90 (1H, dd, J=3.5, 5.3 Hz, Thienyl-H4), 4.53 (1H, m, NC$\underline{H}$CO), 3.27 (3H, s, CO$_2$C$\underline{H}_3$), 2.97 (1H, dd, J=13.7, 5.3 Hz, C$\underline{H}_2$Ar), 2.77 (1H, dd, J=13.7, 10.3 Hz, C$\underline{H}_2$Ar), 2.62 (7H, s, NHC$\underline{H}_3$ and C$\underline{H}_2$C$\underline{H}_2$CO$_2$Me), 2.50 (3H, m, SC$\underline{H}_2$C$\underline{H}$), 2.06 (1H, s, ^{i}BuC$\underline{H}$), 1.51 (1H, m, $Me_2CHC\underline{H}_2$), 1.29 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 0.99 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 0.82 (3H, d, J=6 Hz, CH(C$\underline{H}_3$)$_2$), and 0.75 (3H, d, J=6 Hz, CH(C$\underline{H}_3$)$_2$).

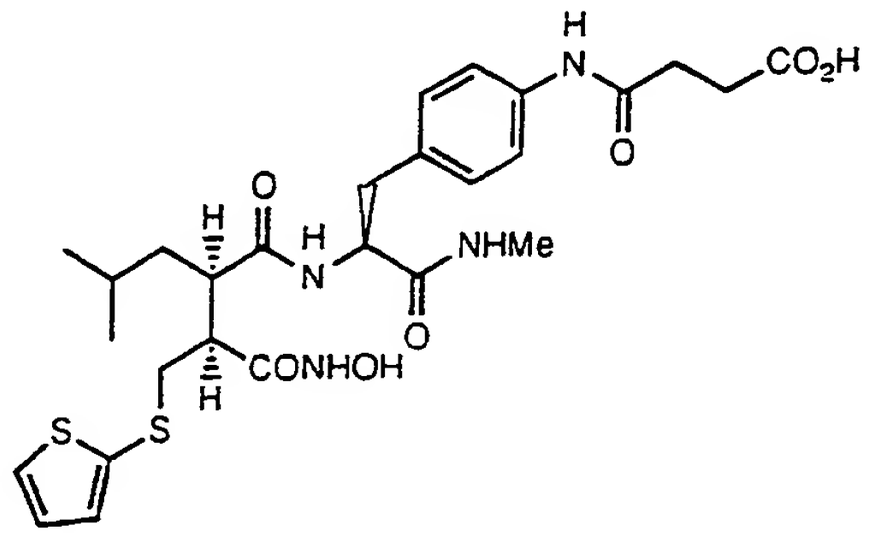
d) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)-phenylalanine-N-methylamide.

[4-Hydroxy-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(N-methylsuccinylamido)- phenylalanine-N-methylamide (0.95g, 1.61 mmol) was taken up in DMF (20 mL) and cooled to 0° while HOBT (0.28g, 2.09 mmol), NMM (0.21g, 2.10 mmol) and WSCDI (0.40g, 2.09 mmol) were added. The reaction was stirred at 0° for 3 hours then hydroxylamine hydrochloride (0.22g, 3.22 mmol) and NMM (0.33g, 3.22 mmol) were added and the reaction allowed to warm to room temperature overnight. The DMF was removed under reduced pressure and the resultant crude oil was taken up in diethyl ether/water (1:1) and the resulting solid collected by filtration. This crude solid was purified by recrystallisation from methanol to give the title compound (0.61g, 1.01 mmol, 62%): Anal. for $C_{28}H_{38}N_4O_7S_2.0.6H_2O$: Requires: C 54.46, H 6.40, N 9.07: Found; C 54.51, H

6.20, N 9.87: ^{1}H-NMR data; δ (DMSO-d_6), 9.89 (1H, s, NHOH), 8.90 (1H, s, CONHOH), 8.23 (1H, d, CHCONHCH), 7.76 (1H, m, CONHCH$_3$), 7.50 (3H, m, Aryl-H and Thienyl-H5), 7.13 (2H, d, J=8.2 Hz, Aryl-H), 6.96 (2H, m, Thienyl-H3,4), 4.40 (1H, m, NHCHCO), 3.57 (3H, s, CO_2CH_3), 2.78 (2H, m, CHCH_2Ar), 2.52 (7H, m, CH_2C$H_2$$CO_2CH_3$ and CONHCH_3), 2.45 (2H, m, CHCH_2S and ^{i}BuCH), 2.14 (2H, m, CHCH_2S), 1.32 (2H, m, $(CH_3)_2$CHCH_2), 0.85 (1H, m, $(CH_3)_2$CHCH_2), 0.78 (3H, d, J=6 Hz, CH(CH_3)$_2$), and 0.71 (3H, d, J=6 Hz, CH(CH_3)$_2$): ^{13}C NMR: δ (DMSO-d_6), 172.3, 171.9, 170.8, 168.9, 167.5, 137.2, 133.1, 132.2, 131.8, 128.1, 128.7, 127.0, 118.1, 53.7, 50.8, 45.6, 45.5, 40.01-38.0, 36.5, 30.4, 28.1, 25.0, 24.6, 23.6 and 21.0.

Example 13

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-(4-(4-oxobutanoic acid)-aminophenylalanine-N-methylamide (BB 1030).

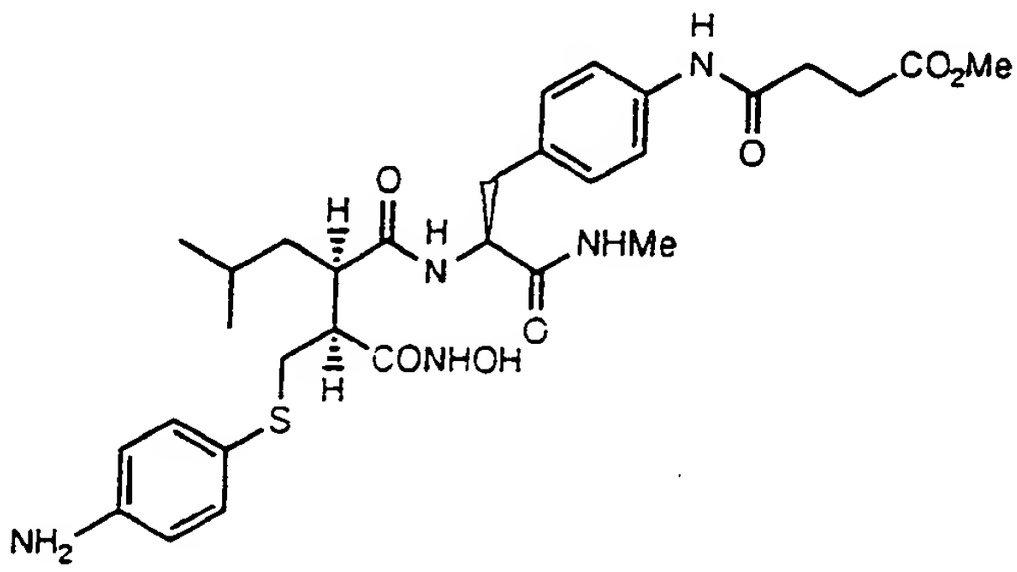


[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)-phenylalanine-N-methylamide (147mg, 0.24 mmol) was suspended in methanol/water and lithium hydroxide (21 mg, 0.50 mmol) added. After six hours at room temperature the reaction was complete and the solution was neutralised with 1M hydrochloric acid. Removal of the sovents gave the title compound as a white solid (150 mg, 0.24 mmol, 100%):^{1}H-NMR; δ(DMSO-d_6), 10.63 (1H, s, NHOH), 10.17 (1H, s, CONHOH), 8.32 (1H, d, J=8.3 Hz, CONHCH), 7.87 (1H, m, CONHCH$_3$), 7.50 (3H, m, Aryl-H and Thienyl-H5), 7.13 (2H, d, J=8.4 Hz, Aryl-H), 6.96 (2H, m, Thienyl-H3,4), 4.40 (1H, m, NHCHCO), 2.77 (2H, m, CHCH_2Ar), 2.52 (7H, m, CH_2C$H_2$$CO_2CH_3$ and CONHCH_3), 2.46 (2H, m, CHCH_2S and ^{i}BuCH), 2.17 (2H, m, CHCH_2S), 1.32 (2H, m, $(CH_3)_2$CHCH_2), 0.83 (1H, m, $(CH_3)_2$CHCH_2), 0.81 (3H, d, J=6 Hz, CH(CH_3)$_2$), and 0.73 (3H, d, J=6 Hz, CH(CH_3)$_2$): ^{13}C NMR: δ (DMSO-d_6),174.1, 171.9, 171.0, 169.9, 167.5, 137.4, 133.1, 132.3, 131.6, 129.0,

128.7, 127.2, 118.0, 54.8, 45.6, 45.5, 40.0, 38.4, 36.5, 31.6, 30.0, 25.0, 24.6, 23.6, and 21.0.

Example 14

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)-phenylalanine-N-methylamide (BB 1033)



a) [4-Hydroxy-2R-isobutyl-3S-(4-aminophenylthiomethyl)-succinyl]-L-4-(N-methylsuccinylamido)-phenylalanine-N-methylamide

[Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(N-methylsuccinyl amido)-phenylalanine-N-methylamide (1.0g, 2.1 mmol) was treated with 4-aminothiophenol as described in example 12c to give the title compound (0.64g, 1.06 mmol, 51%): ^{1}H-NMR; δ (Methanol-d_4), 7.49 (2H, d, J=8.5 Hz, Aryl-H), 7.17 (2H, d, J=8.5 Hz, Aryl-H), 6.96 (2H, d, J=8.5 Hz, Aryl-H), 6.54 (2H, d, J=8.5 Hz, Aryl-H), 4.54 (1H, dd, J=10.1, 5.3 Hz, NC$\underline{H}$CO), 3.60 (3H, s, $CO_2C\underline{H}_3$), 2.97 (1H, dd, J=14.9, 5.2 Hz, $C\underline{H}_2$Ar), 2.80 (1H, bd, $C\underline{H}_2$Ar), 2.63 (7H, s, NHC$\underline{H}_3$ and $C\underline{H}_2C\underline{H}_2CO_2$Me), 2.42 (3H, m, $SC\underline{H}_2C\underline{H}$), 2.11 (1H, m, ^{i}BuC$\underline{H}$), 1.49 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.28 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 0.97 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 0.82 (3H, d, J=6 Hz, $CH(C\underline{H}_3)_2$), and 0.75 (3H, d, J=6 Hz, $CH(C\underline{H}_3)_2$).

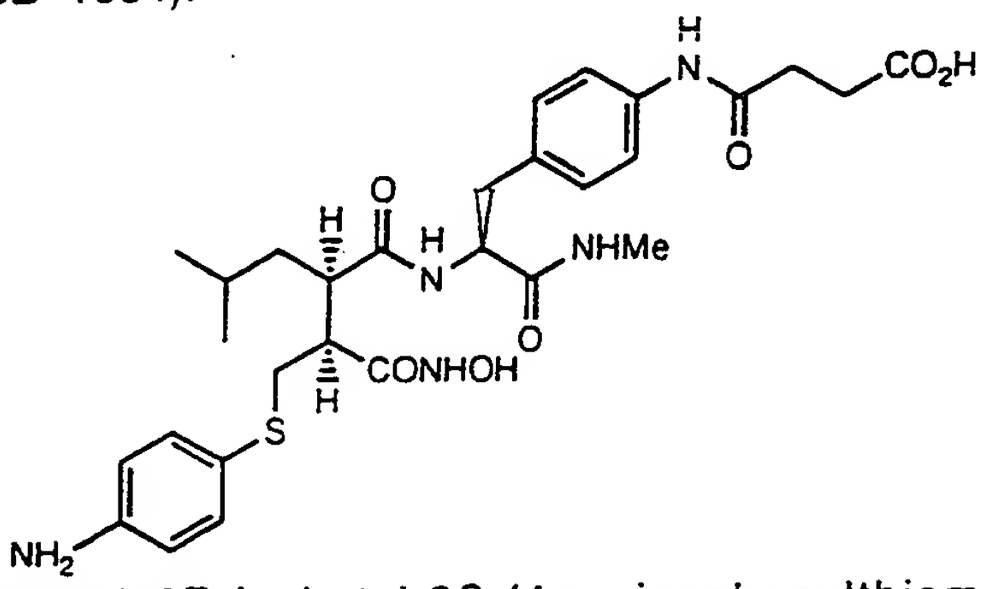
b) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)- phenylalanine-N-methylamide

[4-Hydroxy-2R-isobutyl-3S-(4-aminophenylthiomethyl)-succinyl]-L-4-(N-methylsuccinylamido)-phenylalanine-N-methylamide (0.61g, 1.02 mmol) was coupled with hydroxylamine as described in example 12d to produce the title compound which was recrystallised from ethyl acetate (0.42g,

0.68 mmol, 67%):^{1}H-NMR; δ (Methanol-d_4), 7.47 (1H, d, J=8.4 Hz, CONHCH), 7.13 (2H, d, J=8.4 Hz, Aryl-H), 6.88 (2H, d, J=8.5 Hz, Aryl-H), 6.56 (2H, d, J=8.4 Hz. Aryl-H), 4.58 (1H, m. NHCHCO), 3.60 (3H, s, CO_2CH_3), 2.99 (1H, m, $CHCH_2Ar$),2.79 (1H, m, $CHCH_2Ar$), 2.66 (4H, m, $CH_2CH_2CO_2CH_3$), 2.56 (3H, s, $CONHCH_3$), 2.49 (2H, m, $CHCH_2S$ and ^{i}BuCH), 2.10 (2H, m, $CHCH_2S$), 1.35 (2H, m, $(CH_3)_2CHCH_2$), 0.95 (1H, m, $(CH_3)_2CHCH_2$), 0.81 (3H, d, J=6 Hz, $CH(CH_3)_2$), and 0.73 (3H, d, J=6 Hz, $CH(CH_3)_2$); ^{13}C NMR: δ (Methanol-d_6), 175.5, 174.9, 173.9, 172.3, 171.5, 147.7, 138.9, 134.0, 133.7, 130.6, 123.6, 120.8, 117.1, 56.2, 50.0, 47.6, 41.5, 38.5, 36.4, 32.3, 30.0, 26.9, 26.2, 24.3 and 21.7.

Example 15

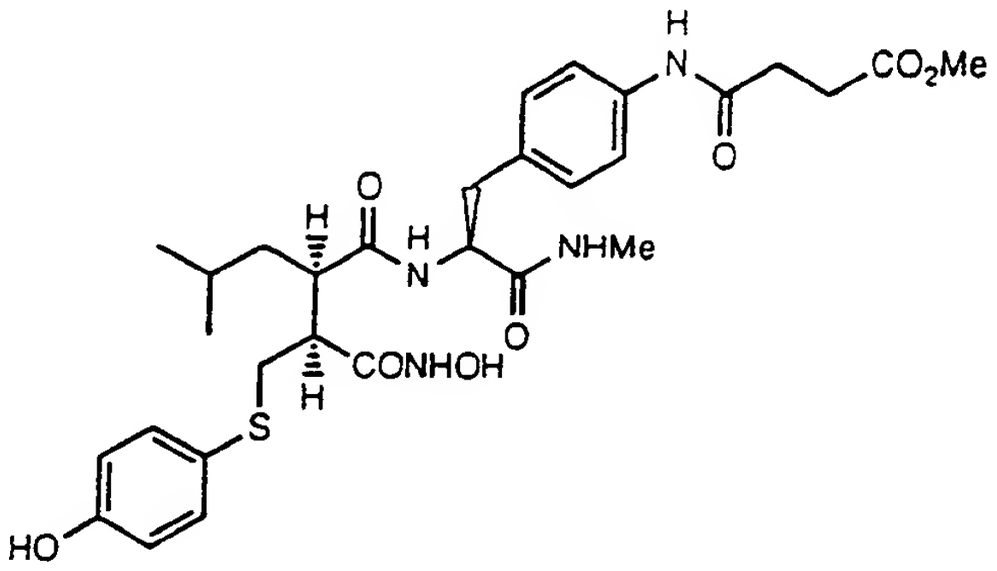
[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthiomethyl)-succinyl]-L-(4-N-(4-(4-oxobutanoic acid)-aminophenylalanine-N-methylamide (BB 1034).



[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)-phenylalanine-N-methylamide (142mg, 0.23mmol) was treated with lithium hydroxide as described in example 13 to give the title compound (140mg, 0.23 mmol,100%):^{1}H-NMR; δ (DMSO-d_6), 10.89 (1H, s, NHOH), 10.54 (1H, s, NHOH), 9.02 (1H, bs, Aryl-NH), 8.31 (1H, d, J=8.1 Hz, CONHCH), 7.82 (1H, m, NHMe), 7.48 (2H, d, J=8.1 Hz, Aryl-H), 7.09 (2H, d, J=8.4 Hz, Aryl-H), 6.88 (2H, d, J=8.3 Hz, Aryl-H), 6.44 (2H, d, J=8.4 Hz, Aryl-H), 4.47 (1H, m, NHCHCO), 2.78 (2H, m, $CHCH_2Ar$), 2.51 (4H, m, $CH_2CH_2CO_2CH_3$), 2.41 (5H, s, $CONHCH_3$, $CHCH_2S$ and ^{i}BuCH), 2.18 (2H, m, $CHCH_2S$), 1.32 (2H, m, $(CH_3)_2CHCH_2$), 0.83 (1H, m, $(CH_3)_2CHCH_2$), 0.77 (3H, d, J=6 Hz, $CH(CH_3)_2$), and 0.73 (3H, d, J=6 Hz, $CH(CH_3)_2$); ^{13}C NMR: δ (DMSO-d_6), 175.3, 172.2, 171.4, 171.0, 167.9, 147.8, 137.7, 133.1, 131.5, 126.8, 118.9, 117.9, 113.9, 53.9, 45.88, 45.6, 39.7-38.4, 37.1, 33.9, 33.3, 25.0, 24.6, 23.7 and 21.0.

Example 16

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)-phenylalanine-N-methylamide (BB 1035)



a) [4-Hydroxy-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)-succinyl]-L-4-(N-methylsuccinylamido)-phenylalanine-N-methylamide

[Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(N-methylsuccinyl amido)-phenylalanine-N-methylamide (1.0g, 2.1 mmol) was treated with 4-hydroxythiophenol as described in example 12c to give the title compound (0.95g, 1.58 mmol, 75%): ^{1}H-NMR; δ (Methanol-d_4), 7.51 (2H, d, J=8.5 Hz, Aryl-H), 7.20 (2H, d, J=8.5 Hz, Aryl-H), 7.02 (2H, d, J=8.5 Hz, Aryl-H), 6.63 (2H, d, J=8.5 Hz, Aryl-H), 4.58 (1H, dd, J=10.1, 5.3 Hz, NC<u>H</u>CO), 3.60 (3H, s, $CO_2C\underline{H}_3$), 2.97 (1H, dd, J=13.1, 5.3 Hz, $C\underline{H}_2$Ar), 2.80 (1H, dd, J=13.0, 4.0 Hz, $C\underline{H}_2$Ar), 2.60 (7H, s, $NHC\underline{H}_3$ and $C\underline{H}_2C\underline{H}_2CO_2$Me), 2.42 (3H, m, $SC\underline{H}_2C\underline{H}$), 2.11 (1H, m, ^{i}BuC<u>H</u>), 1.49 (1H, m, $Me_2CHC\underline{H}_2$), 1.28 (1H, m, $Me_2C\underline{H}CH_2$), 0.97 (1H, m, $Me_2CHC\underline{H}_2$), 0.82 (3H, d, J=6 Hz, $CH(C\underline{H}_3)_2$), and 0.75 (3H, d, J=6 Hz, $CH(C\underline{H}_3)_2$).

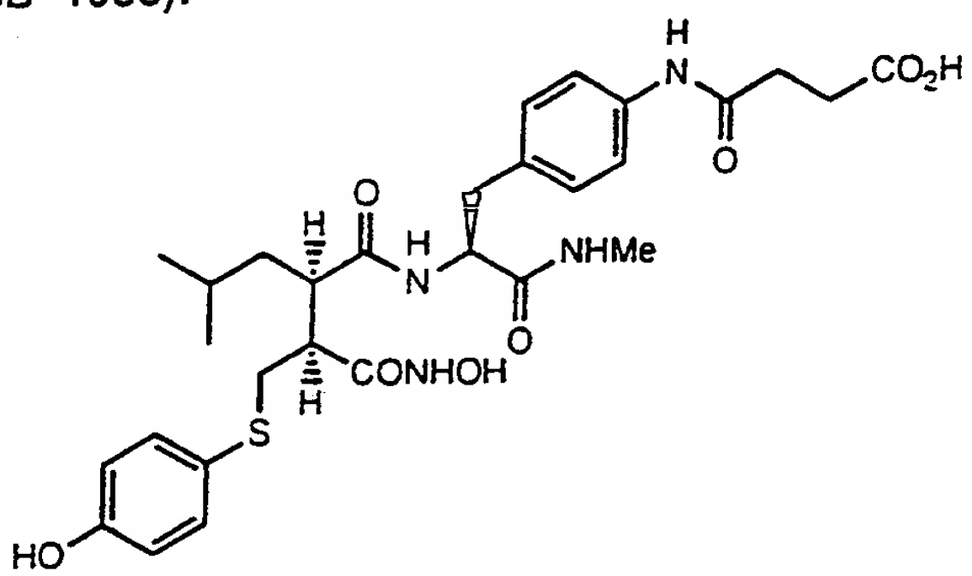
b) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)- phenylalanine-N-methylamide

[4-Hydroxy-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)-succinyl]-L-4-(N-methylsuccinylamido)-phenylalanine-N-methylamide (0.95g, 1.58 mmol) was coupled with hydroxylamine as described in example 12d to produce the title compound (0.40g, 0.64 mmol, 41%):^{1}H-NMR; δ (Methanol-d_4), 7.47 (1H, d, J=8.3 Hz, Aryl-H), 7.19 (2H, d, J=8.4 Hz, Aryl-H), 6.92 (2H, d, J=8.6 Hz, Aryl-H), 6.61 (2H, d, J=8.4 Hz, Aryl-H), 4.56 (1H, m, NHC<u>H</u>CO), 3.57 (3H, s, $CO_2C\underline{H}_3$), 3.01 (1H, m, $CHC\underline{H}_2$Ar), 2.80 (1H, m, $CHC\underline{H}_2$Ar), 2.64

(4H, m, C<u>H</u>$_2$C<u>H</u>$_2$CO$_2$CH$_3$), 2.56 (3H, s, CONHC<u>H</u>$_3$), 2.50 (2H, m, C<u>H</u>CH$_2$S and ^{i}BuC<u>H</u>), 2.06 (2H, m, CHC<u>H</u>$_2$S), 1.29 (2H, m, (CH$_3$)$_2$C<u>H</u>C<u>H</u>$_2$), 0.95 (1H, m, (CH$_3$)$_2$CHC<u>H</u>$_2$), 0.81 (3H, d, J=6 Hz, CH(C<u>H</u>$_3$)$_2$), and 0.73 (3H, d, J=6 Hz, CH(C<u>H</u>$_3$)$_2$); ^{13}C NMR: δ (Methanol-d$_4$),172.3, 172.1, 170.9, 168.9, 167.9, 137.2, 132.0, 131.9, 128.7, 123.4, 117.9, 115.3, 53.7, 50.8, 48.7, 39.4-38.7, 36.5, 35.2, 30.4, 28.1, 25.0, 24.6, 23.6 and 21.0.

Example 17

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)-succinyl]-L-(4-N-(4-(4-oxobutanoic acid)-aminophenylalanine-N-methylamide (BB 1036).

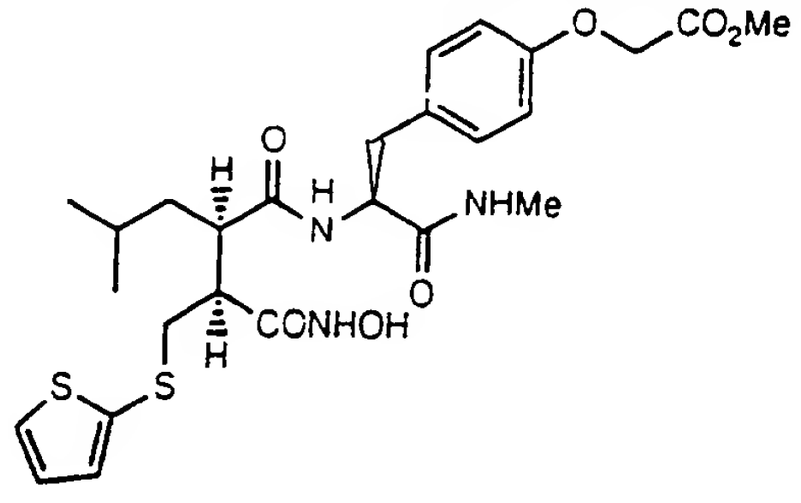


[4-(N-Hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenylthiomethyl)-succinyl]-L-(4-N-(methyl succinylamido)-phenylalanine-N-methylamide (153mg, 0.25mmol) was treated with lithium hydroxide as described in example 13 to give the title compound (150mg, 0.24 mmol,99%):^{1}H-NMR; δ (Methanol-d$_4$), 7.47 (2H, d, J=8.3 Hz, Aryl-H), 7.19 (2H, d, J=8.3 Hz, Aryl-H), 6.92 (2H, d, J=8.6 Hz, Aryl-H), 6.61 (2H, d, J=8.6 Hz, Aryl-H), 4.57 (1H, m. NHC<u>H</u>CO), 2.96 (1H, m, CHC<u>H</u>$_2$Ar),2.81 (1H, m, CHC<u>H</u>$_2$Ar), 2.65 (4H, m, C<u>H</u>$_2$C<u>H</u>$_2$CO$_2$CH$_3$), 2.48 (5H, s, CONHC<u>H</u>$_3$, C<u>H</u>CH$_2$S and ^{i}BuC<u>H</u>), 2.10 (2H, m, CHC<u>H</u>$_2$S), 1.36 (2H, m, (CH$_3$)$_2$C<u>H</u>C<u>H</u>$_2$), 0.97 (1H, m, (CH$_3$)$_2$CHC<u>H</u>$_2$), 0.77 (3H, d. J=6 Hz, CH(C<u>H</u>$_3$)$_2$), and 0.73 (3H, d, J=6 Hz, CH(C<u>H</u>$_3$)$_2$); ^{13}C NMR: δ (Methanol-d$_4$), 180.1, 175.5, 173.9, 173.8, 171.4, 157.8, 139.0, 134.6, 133.9, 130.6, 125.5, 120.9, 117.0, 56.20, 50.01-47.8. 41.5, 38.5, 36.2, 34.5, 33.8, 26.9. 26.2, 24.5 and 21.7.

Example 18

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-

4-(oxymethylcarboxymethyl)-phenylalanine-N-methylamide (BB 943)



a) N-Boc-Tyrosine-N-methylamide.

N-Boc-O-benzyltyrosine-N-methylamide (44.3g, 115 mmol) was dissolved in 10% cyclohexene/ethanol (500 mL), 10% palladium on charcoal (4.5g) added and the mixture refluxed for 3 hours. Filtration to remove the catalyst and solvent removal gave the title compound (30.8g, 105 mmol, 91%).

b) N-Boc-4-(oxymethylcarboxybenzyl)phenylalanine-N-methylamide.

N-Boc-Tyrosine-N-methylamide (30.7g, 104 mmol) was dissolved in acetone (anhydrous, 500 mL), sodium carbonate (13.3g, 125 mmol) and benzylbromoacetate (35.9g, 157 mmol) were added and the mixture refluxed under argon for 4 days. The mixture was filtered, the solvent removed and the residual oil purified by column chromatography using methanol/DCM (2%) as eluant to give the title compound (36.1g, 81.7 mmol. 78%).

c) N-Boc-4-(oxymethylcarboxymethyl)phenylalanine-N-methylamide.

N-Boc-4-(oxymethylcarboxybenzyl)phenylalanine-N-methylamide (19.7g, 55.8 mmol) was taken up in 10% cyclohexene/ethanol (250 mL), 10% palladium on charcoal (2.6 g) added and the mixture refluxed for one hour. Removal of the catalyst by filtration then evaporation of the solvents gave the acid as a white foam (19.7g, 55.8 mmol, 98%). This crude acid was dissolved in DMF (200 mL) and stirred at 0° while potassium carbonate (8.48g, 61 mmol) and methyl iodide (5.21 mL, 83.6 mmol) were added. The mixture was stirred at 0° for 2 hours and at room temperature for one hour. The reaction was filtered to remove inorganic solids, the DMF evaporated under vacuum, then the residue taken up in DCM. The organic layer was washed with brine, dried over magnesium sulphate and finally

the solvent removed to give the title ester as a white solid (18.5g, 50.5 mmol, 91%):^{1}H-NMR; δ ($CDCl_3$), 7.11 (2H, d, J= 8.6 Hz, Aryl-H), 6.83 (2H, d, J= 8.6 Hz, Aryl-H), 6.03 (1H, m, NHMe), 5.14 (1H, bd, NHBoc), 4.60 (2H, s, CH_2CO_2Me), 4.25 (1H, q, J=7.0 Hz), 3.80 (3H, s, CO_2CH_3), 2.98 (2H, bd, J=7 Hz, CH_2Ar), 2.71 (3H, d, $NHCH_3$), and1.40 (9H, s, $C(CH_3)_3$).

d) [4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-(oxymethylcarboxymethyl)phenylalanine-N-methylamide.

N-Boc-4-(oxymethylcarboxymethyl)phenylalanine-N-methylamide (18.5g, 50.5 mmol) was taken up in DCM/TFA (1:1. 100 mL) and left overnight at 4°. Solvent removal gave the amine as the TFA salt contaminated with excess TFA. This mixture was dissolved in DMF (100 mL), cooled to 0°. NMM (14.6g, 145 mmol) and benzyl (2-benzyloxycarbonyl-5-methyl-3R-pentafluorophenoxycarbonyl)-hexanoate (85.5g, 150 mmol) were added and the reaction stirred at room temperature for 72 hours. The DMF was removed under vacuum and the residual oil taken up in DCM, washed with 2M sodium carbonate, 2M hydrochloric acid and saturated brine then dried over magnesium sulphate. The solution was filtered, the solvent evaporated and the resultant oil purified by column chromatography (silica gel, 30 - 53% ethyl acetate in DCM) to give the title compound as a white foam (17.6 g, 27.3 mmol, 54%):^{1}H-NMR; δ ($CDCl_3$), 7.40 -7.17 (10H, m, CO_2CH_2Ph), 7.12 (2H, d, J= 8.6 Hz, Aryl-H), 6.82 (2H, d, J= 8.6 Hz, Aryl-H), 6.67 (1H, d, J=7.8 Hz, NHCH), 5.94 (1H, m, NHMe), 5.22 - 5.04 (3H, m, CO_2CH_2Ph and $CH(CO_2CH_2Ph)_2$), 4.60 (2H, s, CH_2CO_2Me), 4.48 (1H, q, J=7.0 Hz), 3.80 (3H, s, CO_2CH_3), 3.02 - 2.90 (3H, m, CH_2Ar, and ^{i}BuCH), 2.65 (3H, d, J=4.7 Hz, $NHCH_3$), 1.54 (1H, m, $(CH_3)_2CHCH_2$), 1.35 (1H, m, $(CH_3)_2CHCH_2$), 1.04 (1H, m, $(CH_3)_2CHCH_2$), 0.76 (3H, d, J=6.5 Hz, $CH(CH_3)_2$), and 0.74 (3H, d, J=6.5 Hz, $CH(CH_3)_2$).

e) [Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(oxymethylcarboxymethyl)-phenylalanine-N-methylamide

[4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-(oxymethylcarboxymethyl)phenylalanine-N-methylamide (17.6g, 27.3 mmol) was treated as described in example 12b to yeild the title compound (6.70g, 15.4 mmol, 56%):^{1}H-NMR; δ (Methanol-d_4), 7.78 (1H, bd, J=7.2 Hz, CONHCH), 7.10 - 6.75 (5H, m, Aryl-H and NHMe), 6.19 (1H, d, J= 3.0 Hz, CH_2=C), 5.58 (1H, d, J= 3.6 Hz, CH_2=C), 4.63 (2H, s, CH_2CO_2Me), 4.48 (1H, m, NHCHCO), 3.74 (3H, s, CO_2CH_3), 3.52 (1H, m, ^{i}BuCH), 3.00 - 2.78 (2H,

m, C$\underline{H}_2$Aryl), 2.65 (3H, s, NHC$\underline{H}_3$), 1.63 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.40 (1H, m, $(CH_3)_2C\underline{H}CH_2$), and 0.87 - 0.80 (7H, m + 2xd, J=6.5 Hz, $(CH_3)_2CHC\underline{H}_2$ and $CH(C\underline{H}_3)_2$).

f) [4-Hydroxy-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(oxymethylcarboxymethyl)- phenylalanine-N-methylamide.

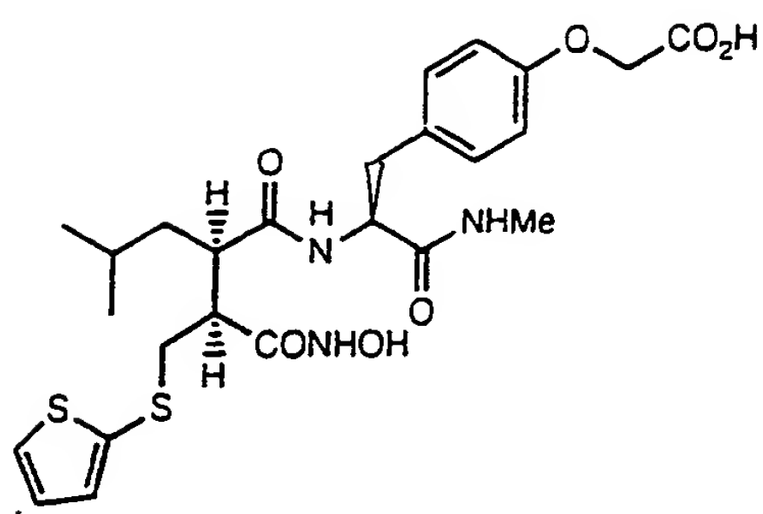
[Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(oxymethylcarboxymethyl)-phenylalanine-N-methylamide (4.77g, 11.0 mmol) was treated with thiophene-2-thiolt as described in example 12c to give the title compound as a white solid (1.90g, 3.46 mmol, 31%): ^{1}H-NMR; δ (DMSO-d_6), 8.35 (1H, bq, N$\underline{H}$Me) 7.96 (1H, d, J= 8.5, CON$\underline{H}$CH), 7.54 (1H, m, Thienyl-H5),7.18 (2H, d, J=8.5 Hz, Aryl-H), 7.00 (2H, m, Thienyl-H3,4), 6.81 (2H, d, J=8.5 Hz, Aryl-H), 4.71 (2H, s, OC$\underline{H}_2CO_2$Me), 4.40 (1H, m, NC$\underline{H}$CO), 3.68 (3H, s, $CO_2C\underline{H}_3$), 2.95 - 2.64 (2H, m, C$\underline{H}_2$Ar), 2.58 (3H, d, J=5.0 Hz, NHC$\underline{H}_3$) 2.37 (2H, m, SC$\underline{H}_2$CH), 2.14 (1H, s, ^{i}BuC$\underline{H}$), 1.42 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 1.23 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 0.99 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 0.79 (3H, d, J=6 Hz, $CH(C\underline{H}_3)_2$), and 0.76 (3H, d, J=6 Hz, $CH(C\underline{H}_3)_2$).

g) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-(oxymethylcarboxymethyl)-phenylalanine-N-methylamide.

[4-Hydroxy-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(oxymethylcarboxymethyl)-phenylalanine-N-methylamide (1.90g, 3.46 mmol) was treated as described in example 12d to give the title compound (0.92g, 1.62 mmol, 47%): ^{1}H-NMR; δ (DMSO-d_6), 10.56 (1H, s, N$\underline{H}$OH), 8.89 (1H, s, CONHO$\underline{H}$), 8.24 (1H, d, CHCON$\underline{H}$CH), 7.79 (1H, m, CON$\underline{H}CH_3$), 7.52 (1H, m, Thienyl-H5), 7.17 (2H, d, J=8.4 Hz, Aryl-H), 6.93 (2H, m, Thienyl-H3,4), 6.78 (2H, d, J=8.4 Hz, Aryl-H), 4.69 (2H, s, OC$\underline{H}_2CO_2$Me), 4.42 (1H, m, NHC$\underline{H}$CO), 3.68 (3H, s, CO_2CH_3), 2.78 (2H, m, CHC$\underline{H}_2$Ar), 2.55 (3H, d, J=4.5 Hz, CONHC$\underline{H}_3$), 2.48 (2H, m, C$\underline{H}CH_2$S and ^{i}BuC$\underline{H}$), 2.08 (2H, m, CHC$\underline{H}_2$S), 1.32 (2H, m, $(CH_3)_2C\underline{H}C\underline{H}_2$), 0.88 (1H, m, $(CH_3)_2CHC\underline{H}_2$), 0.78 (3H, d, J=6 Hz, $CH(C\underline{H}_3)_2$), and 0.71 (3H, d, J=6 Hz, $CH(C\underline{H}_3)_2$): ^{13}C NMR: δ (DMSO-d_6), 171.9, 170.9, 168.8, 167.7, 155.7, 133.1, 131.8, 130.5, 130.2, 128.7, 127.2, 113.6, 64.2, 53.7, 51.3, 45.6, 45.3, 40.05-38.1, 37.7, 36.1, 25.0, 24.6, 23.6 and 21.06

Example 19

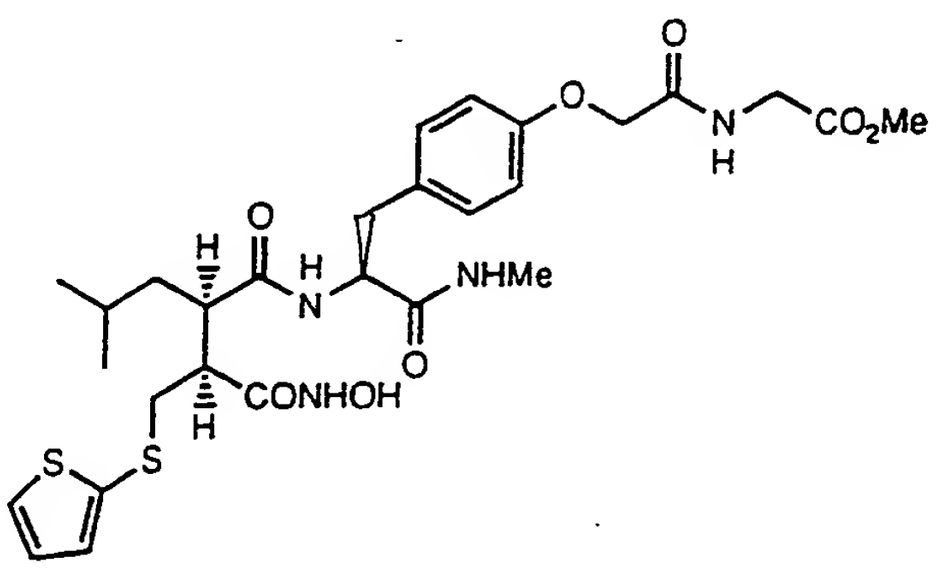
[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-(oxymethylcarboxylic acid)-phenylalanine-N-methylamide (BB 944).



[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-(4-N-(oxymethylcarboxymethyl)-phenylalanine-N-methylamide (0.42g, 0.75 mmol) was treated with lithium hydroxide as described in example 13 to give the title compound (0.42g, 0.75 mmol, 100%) as a white solid: ^{1}H-NMR; δ (D_2O), 7.41 (1H, m, Thienyl-H5), 7.22 (2H, d, J=8.4 Hz, Aryl-H), 6.97 (2H, m, Thienyl-H3,4), 6.89 (2H, d, J=8.4 Hz, Aryl-H), 4.48 (1H, m, NHC<u>H</u>CO), 4.40 (2H, s, OC<u>H$_2$</u>CO$_2$Me), 3.05 (1H, m, CHC<u>H$_2$</u>Ar), 2.74 (1H, m, CHC<u>H$_2$</u>Ar), 2.65 (3H, d, J=4.5 Hz, CONHC<u>H$_3$</u>), 2.38 (2H, m, C<u>H</u>CH$_2$S and iBuC<u>H</u>), 2.03 (1H, m, CHC<u>H$_2$</u>S), 1.78 (1H, m, CHC<u>H$_2$</u>S), 1.23 (2H, m, (CH$_3$)$_2$C<u>H</u>C<u>H$_2$</u>), 0.98 (1H, m, (CH$_3$)$_2$CHC<u>H$_2$</u>), 0.78 (3H, d, J=6 Hz, CH(C<u>H$_3$</u>)$_2$), and 0.71 (3H, d, J=6 Hz, CH(C<u>H$_3$</u>)$_2$): ^{13}C NMR: δ (D_2O),176.9, 175.5, 173.6, 168.3, 157.0, 133.3, 123.4, 130.6, 129.9, 128.0, 115.0, 66.9, 55.4, 46.7, 46.0, 40.0, 36.6, 36.4, 26.0, 25.6, 23.2, and 20.8.

Example 20

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (BB 888)



a) N-Boc-4-(oxymethylcarboxylic acid)-phenylalanine-N-methylamide

N-Boc-4-(oxymethylcarboxybenzyl)phenylalanine-N-methylamide (35.5g, 80.3 mmol) was dissolved in 20% cyclohexene in ethanol (400 mL), 7.1g 10% palladium on charcoal added and the mixture heated under reflux for 15 minutes. The catalyst was removed by filtration and the solvent evaporated to leave the title compound (28.5g, 80.5 mmol, 100%):^{1}H-NMR; δ (Methanol-d_4), 7.09 (2H, d, J=8.6 Hz, Aryl-H), 6.81 (2H, d, J=8.6 Hz, Aryl-H), 4.56 (2H, s, OC$\underline{H}_2$CO$_2$H), 4.18 (1H, m, NHC$\underline{H}$CO), 2.95 - 2.72 (2H, m, C$\underline{H}_2$Ar), 2.62 (3H, s, CONHC$\underline{H}_3$), and 1.32 (9H, s, C(CH_3)$_3$).

b) N-Boc-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide.

N-Boc-4-(oxymethylcarboxylic acid)-phenylalanine-N-methylamide (7.47g, 21.2 mmol) was taken up in DMF (25 mL) and cooled to 0°. To this solution was added, pentafluorophenol (7.80g, 42.4 mmol), glycine methyl ester (from the hydrochloride salt, 3.19g, 25.4 mmol) and WSCDI (4.88g, 25.4 mmol) and the mixture stirred at room temperature overnight. The solvent was removed by evaporation and the residual oil taken up in DCM which was then sequentially washed with 2M sodium carbonate solution, 2M hydrochloric acid solution and saturated brine. The separated organic layer was dried over magnesium sulphate and the solvent evaporated to leave the title compound (7.08g, 16.7 mmol, 79%):^{1}H-NMR; δ ($CDCl_3$), 7.12 (2H, d, J=8.6 Hz, Aryl-H), 6.84 (2H, d, J=8.6 Hz, Aryl-H), 6.11 (1H, bq, CONHMe), 5.17 (1H, bd, CONHCH), 4.48 (2H, s, OC$\underline{H}_2$CO$_2$H), 4.28 (1H, m, NHC$\underline{H}$CO), 4.12 (2H, bd, NHC$\underline{H}_2$CO$_2$Me), 3.76 (3H, s, CO$_2$CH_3), 2.96 (2H, m, C$\underline{H}_2$Ar), 2.72 (3H, d, J=4.8 Hz, CONHC$\underline{H}_3$), and 1.38 (9H, s, C(CH_3)$_3$).

c) [4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)phenylalanine-N-methylamide.

N-Boc-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (5.35g, 12.6 mmol) was dissolved in TFA/DCM (1:1, 100 mL) and stood overnight at 4°. Solvent removal gave an oil which was dissolved in DCM and washed with 2M sodium carbonate, dried over magnesium sulphate and the solvent removed to leave the free amine as a yellow solid (3.71g, 11.1 mmol, 88%). This was coupled with benzyl (2-benzyloxycarbonyl-5-methyl-3R-pentafluorophenoxycarbonyl)-hexanoate (12.4g, 21.9 mmol) as described in example 18d to give the title compound (6.60g, 9.38 mmol, 86%):^{1}H-NMR; δ ($CDCl_3$), 7.35 - 7.20 (10H, m, Ph), 7.15

(2H, d. J=8.6 Hz, Aryl-H), 6.84 (2H, d, J=8.6 Hz, Aryl-H), 6.67 (1H, bd, CONHCH), 5.92 (1H, bq, CONHMe), 5.17 - 5.05 (4H, m, $CH(CO_2CH_2Ph)_2$), 4.48 (3H, s + m, OCH_2CO_2H and NHCHCO), 4.12 (2H, bd, $NHCH_2CO_2Me$), 3.80 (1H, d, J=9.3 Hz, $CH(CO_2CH_2Ph)_2$), 3.76 (3H, s, CO_2CH_3), 2.97 (2H, m, CH_2Ar), 2.67 (3H, d, J=4.8 Hz, $CONHCH_3$), 1.54 (1H, m, $(CH_3)_2CHCH_2$), 1.35 (1H, m, $(CH_3)_2CHCH_2$),1.02 (1H, m, $(CH_3)_2CHCH_2$), 0.76 (3H, d, J=6.4 Hz, $CH(CH_3)_2$), and 0.75 (3H, d, J=6.4 Hz, $CH(CH_3)_2$).

d) [Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide

[4-Benzyloxy-3-benzyloxycarbonyl-2R-isobutylsuccinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)phenylalanine-N-methylamide (7.62g, 10.8 mmol) was treated as described in example 12b to yield the title compound (3.77g, 7.67 mmol, 72%):^{1}H-NMR; δ (Methanol-d_4), 7.80 (2H, bm, NH), 7.08 (2H, d, J=8.7 Hz, Aryl-H), 6.86 (2H, d, J=8.7 Hz, Aryl-H), 6.18 (1H, d, J= 3.0 Hz, CH_2=C), 5.59 (1H, d, J= 3.6 Hz, CH_2=C), 4.49 (2H, s, OCH_2CO_2H), 4.45 (1H, m, NHCHCO), 3.99 (2H, s, $NHCH_2CO_2Me$), 3.69 (3H, s, CO_2CH_3), 3.52 (1H , bm, $CHCO_2H$), 2.88 (2H, m, CH_2Ar), 2.65 (3H, d, J=4.8 Hz, $CONHCH_3$), 1.63 (1H, m, $(CH_3)_2CHCH_2$), 1.40 (2H, m, $(CH_3)_2CHCH_2$), 0.86 (3H. d, J=6.2 Hz, $CH(CH_3)_2$), and 0.81 (3H, d, J=6.3 Hz, $CH(CH_3)_2$).

e) [4-Hydroxy-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-pnenylalanine-N-methylamide.

[Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (1.56g, 3.17 mmol) was treated with thiophene-2-thiol as described in example 12c to give the title compound as a white solid (1.30g, 2.14 mmol, 67%): ^{1}H-NMR; δ (Methanol-d_4), 8.39 (1H, bd, J=8.5 Hz, NHCH), 7.85 (1H, m, CONHMe), 7.38 (1H, dd. J=5.3, 1.3 Hz, Thienyl-H5), 7.21 (2H, d, J=8.6 Hz, Aryl-H), 6.98 (1H, dd. J=3.5, 1.3 Hz, Thienyl-H3), 6.94 (2H, d, J=8.7 Hz, Aryl-H), 6.91 (1H, dd. J=5.2, 3.5 Hz, Thienyl-H4), 4.55 (3H, s, OCH_2CO_2H and NHCHCO), 3.96 (2H, s, $NHCH_2CO_2Me$), 3.67 (3H, s, CO_2CH_3), 2.91 (1H, dd, J= 13.9, 5.1 Hz, CH_2Ar), 2.76 (1H, dd, J= 13.9, 5.1 Hz, CH_2Ar), 2.66 (3H, s, $CONHCH_3$), 2.45 (3H, m, SCH_2CH and $CHCO_2H$), 2.16 (1H, m, SCH_2CH), 1.50 (1H, m, $(CH_3)_2CHCH_2$), 1.30 (1H, m, $(CH_3)_2CHCH_2$), 0.98 (1H, m, $(CH_3)_2CHCH_2$), 0.83 (3H, d, J=6.5 Hz. $CH(CH_3)_2$), and 0.76 (3H, d, J=6.3 Hz, $CH(CH_3)_2$).

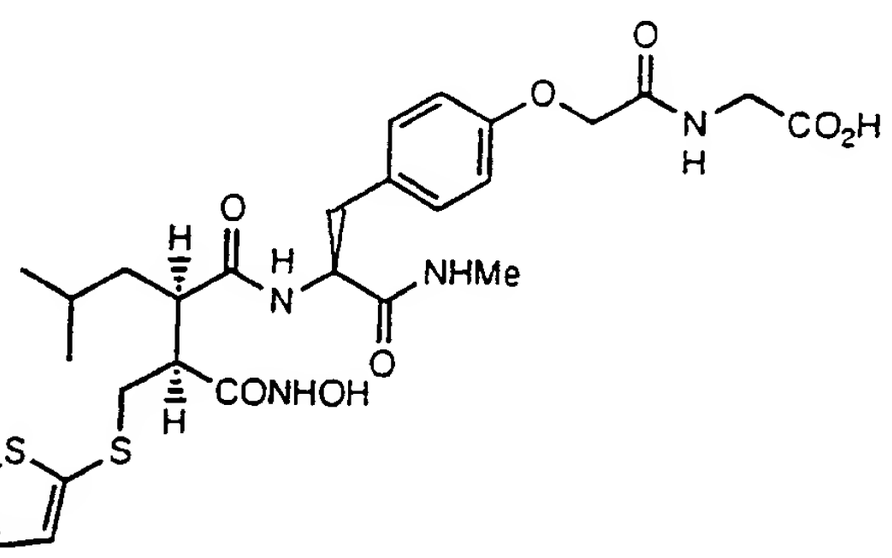
f) [4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-

L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide

[4-Hydroxy-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (1.29g, 2.12 mmol) was treated as described in example 12d to give the title compound as a white solid (0.90g, 1.45 mmol, 68%):Anal. calculated for $C_{28}H_{38}N_4O_8S_2$, Requires, C 54.00, H 6.15, N 9.00; Found, C 54.04, H 6.16, N 8.79: ^{1}H-NMR; δ (DMSO-d_6), 10.55 (1H, s, CONHOH), 8.89 (1H, s, CONHOH), 8.45 (1H, m, CONHCH$_2$), 8.23 (1H, bd, J=8.5 Hz, NHCH), 7.79 (1H, m, CONHMe), 7.51 (1H, dd, J=5.3, 1.3 Hz, Thienyl-H5), 7.19 (2H, d, J=8.6 Hz, Aryl-H), 6.95 (2H, m, Thienyl-H3,4), 6.83 (2H, d, J=8.5 Hz, Aryl-H), 4.47 (2H, s, OCH$_2$CO$_2$Me), 4.45 (1H, m, NHCHCO), 3.92 (2H, s, NHCH$_2$CO$_2$Me), 3.63 (3H, s, CO$_2$CH$_3$), 2.88 (1H, m, SCH$_2$CH), 2.62 (2H, m, CH$_2$Ar), 2.53 (3H, d, J=4.5 Hz, CONHCH$_3$), 2.39 (1H, m, ^{i}BuCH), 2.16 (1H, m, SCH$_2$CH), 1.99 (1H, m, SCH$_2$CH),1.31 (2H, m, (CH$_3$)$_2$CHCH$_2$), 0.83 (1H, m, (CH$_3$)$_2$CHCH$_2$), 0.80 (3H, d, J=6.6 Hz, CH(CH$_3$)$_2$), and 0.76 (3H, d, J=6.6 Hz, CH(CH$_3$)$_2$): ^{13}C-NMR; δ (DMSO-d_6), 172.4, 171.4, 170.0, 168.3, 167.9, 156.1, 132.3, 130.7, 130.1, 129.2, 127.7, 114.4, 66.8, 54.2, 51.7, 46.0, 45.8, 40.5-38.5, 38.1, 36.6, 25.4, 25.0, 24.0 and 21.5

Example 21

[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(oxymethylcarboxyglycine)-phenylalanine-N-methylamide (BB 899).

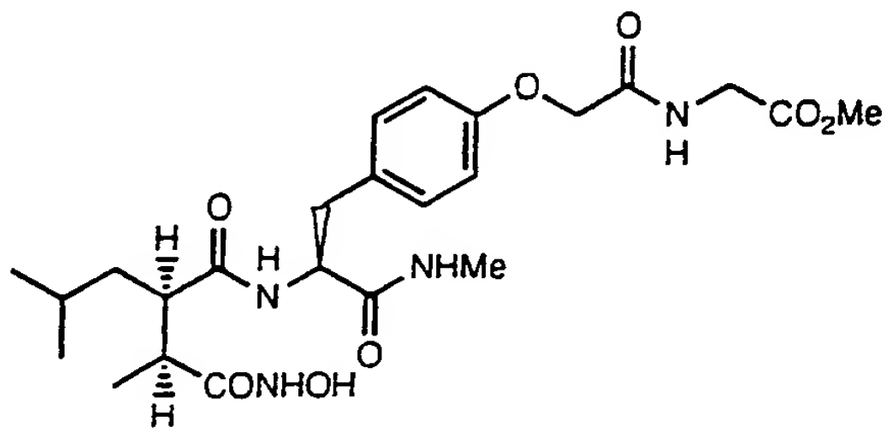


[4-(N-Hydroxyamino)-2R-isobutyl-3S-(2-thienylthiomethyl)-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (0.45g, 0.73 mmol) was treated with lithium hydroxide as described in example 13 to give the title compound (0.41g, 0.67 mmol, 92%): ^{1}H-NMR; δ (D_2O), 7.43 (1H, dd, J=5.3, 1.3 Hz, Thienyl-H5), 7.28 (2H, d, J=8.5 Hz, Aryl-

H), 7.06 (2H, d, J=8.5 Hz, Aryl-H), 6.95 (1H, m, Thienyl-H3), 6.83 (1H, m, Thienyl-H4), 4.70 (1H, m, NHC<u>H</u>CO), 4.58 (2H, s, NHC<u>H</u>$_2$CONH), 3.63 (2H, bs. NHC<u>H</u>$_2$CO$_2$H). 3.12 (1H. m. C<u>H</u>$_2$Ar), 2.79 (1H. m. C<u>H</u>$_2$Ar), 2.68 (3H, s, CONHC<u>H</u>$_3$), 2.21 (2H, m, SCH$_2$C<u>H</u> and ^{i}BuC<u>H</u>), 2.05 (1H, m, SC<u>H</u>$_2$CH), 1.65 (1H. m, SC<u>H</u>$_2$CH),1.19 (2H, m, (CH$_3$)$_2$C<u>H</u>C<u>H</u>$_2$), 0.91 (1H, m, (CH$_3$)$_2$CHC<u>H</u>$_2$), 0.81 (3H. d, J=6.6 Hz, CH(C<u>H</u>$_3$)$_2$), and 0.76 (3H, d, J=6.6 Hz, CH(C<u>H</u>$_3$)$_2$): ^{13}C-NMR; δ (D_2O), 195.6, 176.6, 175.5, 173.8, 171.6, 156.7, 132.8, 132.2, 130.8, 130.6. 129.7, 128.1, 115.5, 66.9, 55.3, 46.8, 46.0, 42.8, 40.0, 36.7, 36.3, 26.5, 26.1, 23.5 and 20.1.

Example 22

[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (BB 877)



a) [4-(N-Benzyloxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide

[Hydroxy-2R-isobutyl-3-ethenylsuccinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (1.05g, 2.14 mmol) was dissolved in ethanol (40 mL), 10% palladium on charcoal added and the mixture subjected to an atmosphere of hydrogen for one hour. The catalyst was removed by filtration and solvent removal gave the saturated compound as a solid (0.99g, 2.00 mmol, 93%). This material (0.97g, 1.96 mmol) was dissolved in DMF/DCM (20%, 10 mL), pentafluorophenol (0.72g, 3.93 mmol), O-benzylhydroxylamine (0.48g, 3.93 mmol), NMM (0.26g, 2.55 mmol) and WSCDI (0.49g, 2.55 mmol) added and the reaction mixture stirred overnight. The preciptated solid was filtered off and the solvent removed from the filtrate to leave a solid which was washed with 1M hydrochloric acid and ethyl acetate. The combined solids were recrystallised from methanol to give the title benzhydroxamate (0.42g,

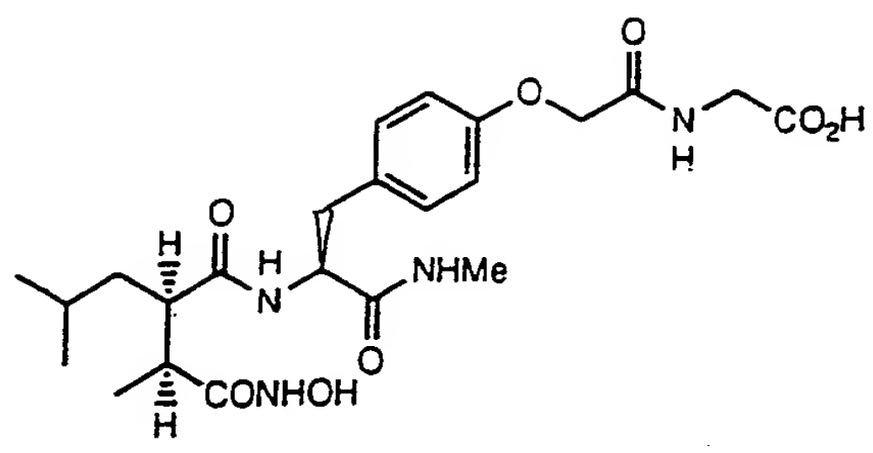
0.70 mmol, 36%): ^{1}H-NMR; δ (DMSO-d_6), 10.98 (1H, s, CONHOBn), 8.48 (1H, m, NHCH$_2$), 8.15 (1H, d, J=9 Hz, NHCH), 7.73 (1H, m, CONHMe), 7.36 (5H, s, Ph), 7.19 (2H, d, J=8.6 Hz, Aryl-H), 6.86 (2H, d, J=8.7 Hz, Aryl-H), 4.74 (2H, s, CH$_2$Ph), 4.46 (3H, s, OCH$_2$CO$_2$Me and NHCHCO), 3.90 (2H, d, J=5.6 Hz, NHCH$_2$CO$_2$Me), 3.63 (3H, s, CO$_2$CH$_3$), 2.89 (1H, m, CH$_2$Ar), 2.73 (1H, m, CH$_2$Ar), 2.56 (3H, d, J=4.5 Hz, CONHCH$_3$), 2.37 (1H, m, CHCONHOBn), 1.91 (1H, m, ^{i}BuCH), 1.30 (2H, m, (CH$_3$)$_2$CHCH$_2$), 0.83 (3H, d, J=6.3 Hz, CH(CH$_3$)$_2$), 0.72 (3H, d, J=6.3 Hz, CH(CH$_3$)$_2$), 0.71 (1H, m, (CH$_3$)$_2$CHCH$_2$), and 0.45 (3H, d, J=6.6 Hz, CHCH$_3$).

b) [4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide

[4-(N-Benzyloxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (0.42g, 0.70 mmol) was hydrogenated as described in example 10c to give the title compound as a solid (0.29g, 0.57 mmol, 82%): Anal. calculated for $C_{24}H_{36}N_4O_8$: Requires, C 56.86, H 7.13, N 11.02; Found, C 56.14, H 7.08, N 10.60: ^{1}H-NMR; δ (DMSO-d_6), 8.70 (1H, s, CONHOH), 8.49 (1H, m, NHCH$_2$), 8.18 (1H, d, J=8.5 Hz, NHCH), 7.73 (1H, m, CONHMe), 7.19 (2H, d, J=8.5 Hz, Aryl-H), 6.85 (2H, d, J=8.6 Hz, Aryl-H), 4.47 (1H, m, NHCHCO), 4.48 (2H, s, OCH$_2$CO$_2$Me), 3.89 (2H, d, J=5.9 Hz, NHCH$_2$CO$_2$Me), 3.63 (3H, s, CO$_2$CH$_3$), 2.89 (1H, m, CH$_2$Ar), 2.69 (1H, m, CH$_2$Ar), 2.58 (3H, d, J=4.5 Hz, CONHCH$_3$), 2.39 (1H, m, CHCONHOBn), 1.98 (1H, m, ^{i}BuCH), 1.32 (2H, m, (CH$_3$)$_2$CHCH$_2$), 0.88 (1H, m, (CH$_3$)$_2$CHCH$_2$), 0.83 (3H, d, J=6.5 Hz, CH(CH$_3$)$_2$), 0.72 (3H, d, J=6.5 Hz, CH(CH$_3$)$_2$), and 0.48 (3H, d, J=6.6 Hz, CHCH$_3$): ^{13}C-NMR; δ (DMSO-d_6), 172.8, 171.1, 170.7, 169.6, 167.9, 155.7, 130.6, 129.7, 113.9, 66.6, 53.7, 51.3, 46.2, 39.9-38.0, 36.1, 25.0, 24.8, 23.6, 21.1 and 15.6.

Example 23

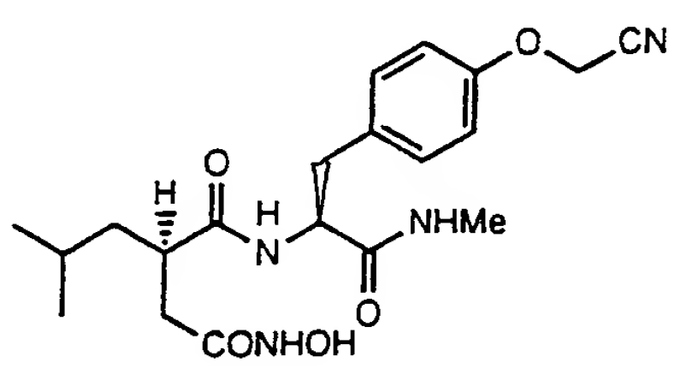
[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-4-(oxymethylcarboxyglyine)-phenylalanine-N-methylamide



[4-(N-Hydroxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide (0.11g, 0.22 mmol) was treated with lithium hydroxide as described in example 13 to give the title compound (0.09g, 0.18 mmol, 83%): ^{1}H-NMR; δ (D_2O), 7.19 (2H, d, J=8.5 Hz, Aryl-H), 6.92 (2H, d, J=8.6 Hz, Aryl-H), 4.56 (2H, s, $OC\underline{H_2}CO_2Me$), 4.51 (1H, m, $NHC\underline{H}CO$), 3.80 (2H, s, $NHC\underline{H_2}CO_2Me$), 2.96 (2H, m, $C\underline{H_2}Ar$), 2.61 (3H, s, $CONHC\underline{H_3}$), 2.42 (1H, m, $C\underline{H}CONHOBn$), 2.11 (1H, m, ^{i}BuC$\underline{H}$), 1.31 (2H, m, $(CH_3)_2C\underline{H}C\underline{H_2}$), 0.95 (1H, m, $(CH_3)_2CHC\underline{H_2}$), 0.83 (3H, d, J=6.5 Hz, $CH(C\underline{H_3})_2$), 0.75 (3H, d, J=6.5 Hz, $CH(C\underline{H_3})_2$), and 0.61 (3H, d, J=6.6 Hz, $CHC\underline{H_3}$): ^{13}C-NMR; δ (D_2O), 195.6, 176.6, 175.5, 173.8, 171.6, 156.7, 132.8, 132.2, 130.8, 130.6, 129.7, 128.1, 115.5, 66.9, 55.3, 46.8, 46.0, 42.8, 40.0, 36.7, 36.3, 26.5, 26.1, 23.5 and 20.1.

Example 24

[4-(N-Hydroxyamino)-2R-isobutyl-succinyl]-L-4-(oxymethylnitrile)-phenylalanine-N-methylamide.



a) [4-t-Butoxy-2R-isobutylsuccinyl]-L-(4-oxymethylnitrile)-phenylalanine-N-methylamide.

[4-t-Butoxy-2R-isobutylsuccinyl]-L-(4-hydroxy)-phenylalanine-N-methylamide (see example 1g, 0.50g, 1.2 mmol) was dissolved in dry methyl ethyl ketone (20 mL) and sodium carbonate (0.16g, 1.48 mmol) was added. Bromoacetonitrile (0.22g, 1.84 mmol) was added dropwise and the

reaction heated at reflux overnight after which time a second aliquot of bromoacetonitrile was added (0.22g, 1.84 mmol) and the mixture heated at reflux for a further 18 hours. The solvents were removed under vacuum and the residue taken up in DCM/hexane and filtered then purified by column chromatography (silica gel, 5% methanol/DCM) to give recovered starting material (0.21g) along with the title compound (0.38g, 0.85 mmol. 71%): ^{1}H-NMR; δ ($CDCl_3$), 7.08 (2H, d, J=8.6 Hz, Aryl-H), 6.76 (2H, d, J=8.6 Hz, Aryl-H), 6.34 (1H, d, J= 7.9 Hz, CONHCH), 5.91 (1H, m, CONHMe), 4.78 (2H, s, OCH_2CN), 4.49 (1H, m, NHCHCO), 3.06 (1H, dd, J=6.2, 13.8 Hz, CH_2Ar), 2.97 (1H, dd, J=7.9, 13.8 Hz, CH_2Ar), 2.70 (3H, d, J=4.8 Hz, CONHMe), 2.61 (1H, m, ^{i}BuCH), 2.49 (1H, dd, J= 4.2, 16.1 Hz, $CH_2CO_2{}^t$Bu), 2.40 (1H, dd, 4.2, 16.1 Hz, $CH_2CO_2{}^t$Bu), 1.44 (11H, s + m, $C(CH_3)_3$ and $(CH_3)_2CHCH_2$), 1.25 (1H, m, $(CH_3)_2CHCH_2$), 0.87 (3H, d, J=6.4 Hz, $CH(CH_3)_2$), and 0.84 (3H, d, J=6.4 Hz, $CH(CH_3)_2$).

b) [4-(N-Benzyloxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylnitrile)-phenylalanine-N-methylamide.

[4-t-Butoxy-2R-isobutylsuccinyl]-L-(4-oxymethylnitrile)-phenylalanine-N-methylamide (0.38g, 0.98 mmol) was dissolved in 95% TFA/water and stirred at 0° for 3 hours after which time tlc indicated complete conversion to the acid. Removal of the solvents gave the crude acid which was taken up in DCM (5mL), pentafluorophenol (0.36g, 1.95 mmol), O-benzylhydroxylamine (0.24g, 1.95 mmol), NMM (0.15g, 1.47 mmol) and WSCDI (0.26g, 1.37 mmol) added, and the reaction mixture stirred overnight. The precipitated product was collected by filtration and washed with DCM and dried to give the title compound (0.21g, 0.47 mmol, 48%): ^{1}H-NMR; δ (Methanol-d_4), 8.17 (1H, d, J= 7.9 Hz, CONHCH), 7.91 (1H, m, CONHMe), 7.36 (5H, s, Ph), 7.36 (2H, d, J=8.6 Hz, Aryl-H), 6.90 (2H, d, J=8.6 Hz, Aryl-H), 4.85 (2H, s, OCH_2Ph), 4.77 (2H, s, OCH_2CN), 4.45 (1H, m, NHCHCO), 3.10 (1H, dd, J=6.9, 14.4 Hz, CH_2Ar), 2.87 (1H, dd, J=8.9, 13.8 Hz, CH_2Ar), 2.66 (4H, d + m, J=4.6 Hz, CONHMe and ^{i}BuCH), 2.16 (1H, dd, J= 8.2, 14.6 Hz, $CH_2CO_2{}^t$Bu), 2.01 (1H, dd, 6.4, 14.5 Hz, $CH_2CO_2{}^t$Bu), 1.32 (2H, m, $(CH_3)_2CHCH_2$), 1.06 (1H, m, $(CH_3)_2CHCH_2$), 0.81 (3H, d, J=6.4 Hz, $CH(CH_3)_2$), and 0.77 (3H, d, J=6.4 Hz, $CH(CH_3)_2$).

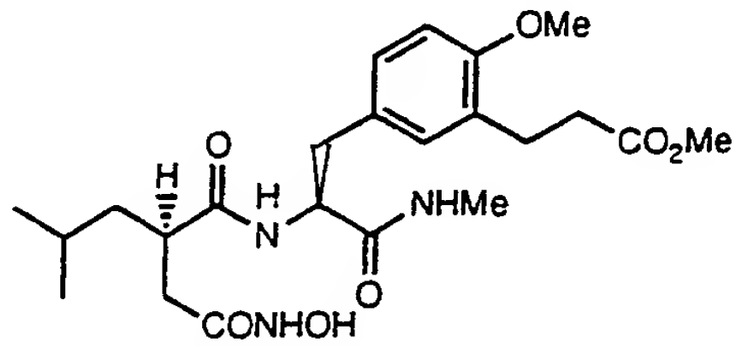
c) [4-(N-Hydroxyamino)-2R-isobutyl-succinyl]-L-4-(oxymethylnitrile)-phenylalanine-N-methylamide.

[4-(N-Benzyloxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylnitrile)-

phenylalanine-N-methylamide (0.21g, 0.47 mmol) was hydrogenated as described in example 10c and purified by recrystallisation from methanol/diethyl ether (0.10g, 0.25 mmol, 53%): ^{1}H-NMR; δ (Methanol-d_4), 7.18 (2H, d, J=8.7 Hz, Aryl-H), 6.92 (2H, d, J=8.7 Hz, Aryl-H), 4.90 (2H, s, OC$\underline{H}_2$CN), 4.42 (1H, m, NHC$\underline{H}$CO), 3.12 (1H, m, C$\underline{H}_2$Ar), 2.64 (4H, s + m, CONHMe and ^{i}BuC$\underline{H}$), 2.18 (1H, dd, J= 8.0, 14.6 Hz, C$\underline{H}_2$CO$_2{}^t$Bu), 2.06 (1H, dd, 6.5, 14.5 Hz, C$\underline{H}_2$CO$_2{}^t$Bu), 1.33 (2H, m, $(CH_3)_2$CHC$\underline{H}_2$), 1.07 (1H, m, $(CH_3)_2$C$\underline{H}$CH$_2$), 0.81 (3H, d, J=6.4 Hz, CH(C$\underline{H}_3$)$_2$), and 0.77 (3H, d, J=6.4 Hz, CH(C$\underline{H}_3$)$_2$): ^{13}C-NMR; δ (Methanol-d_4), 177.1, 174.0, 171.1, 158.0, 133.1, 131.6, 115.8, 56.3, 54.5, 42.6, 37.4, 36.8, 26.8, 26.3, 23.5, and 22.3.

Example 25

[4-(N-Hydroxyamino)-2R-isobutyl-succinyl]-L-3-(1-(2-methoxycarbonyl)-ethyl)-4-methoxy-phenylalanine-N-methylamide (BB 708).



a) [4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-(1-(2-methoxycarbonyl)-ethene)-4-methoxy-phenylalanine-N-methylamide.

[4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-iodo-4-methoxy-phenylalanine-N-methylamide (0.50g, 0.92 mmol) was dissolved in dry acetonitrile (1.5 mL) under argon and methyl acrylate (0.10 mL, 1.15 mmol), triethylamine (0.16 mL, 1.15 mmol), tris-*o*-tolylphosphine (0.07g, 0.23 mmol) and palladium acetate (26 mg, 0.115 mmol) were added, the tube was sealed and heated to 90° overnight. The reaction mixture was cooled, dissolved in ethyl acetate and washed with water. The organic layer was dried over magnesium sulphate, filtered and the solvent removed to give a brown solid which was purified by chromatograpy on silica gel using ethyl acetate as eluant (0.36g, 0.71mmol, 78%): ^{1}H-NMR; δ ($CDCl_3$), 7.95 (1H, d, J=16.2 Hz, ArC$\underline{H}$CHCO$_2$Me), 7.37 (1H, m, Aryl-H), 7.23 (1H, m, Aryl-H), 6.85 (1H, d, J=8.5 Hz, Aryl-H3), 6.54 (1H, d, J=16.2 Hz, ArCHC$\underline{H}$CO$_2$Me), 6.28 (1H, d, J=7.7 Hz, N$\underline{H}$CH), 6.01 (1H, m, CON$\underline{H}$Me), 4.51 (1H, dd, J=7.5, 6.5 Hz, NHC$\underline{H}$CO), 3.87 (3H, s, OC$\underline{H}_3$), 3.80 (3H, s, CO$_2$C$\underline{H}_3$), 3.06 (2H, m, CH$_2$Ar), 2.72 (3H, d, J=4.7 Hz, CONHC$\underline{H}_3$), 2.61 - 2.34 (3H, m, C$\underline{H}_2$CO$_2{}^t$Bu and ^{i}BuC$\underline{H}$), 1.43

(11H, s + m, $C(C\underline{H}_3)_3$ and $(CH_3)_2CHC\underline{H}_2$), 1.20 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 0.87 (3H, d, J=6.3 Hz, $CH(C\underline{H}_3)_2$), and 0.83 (3H, d, J=6.3 Hz, $CH(C\underline{H}_3)_2$).

b) [4-(N-Benzyloxyamino)-2R-isobutyl-succinyl]-L-3-(1-(2-methoxycarbonyl)-ethene)-4-methoxy-phenylalanine-N-methylamide.

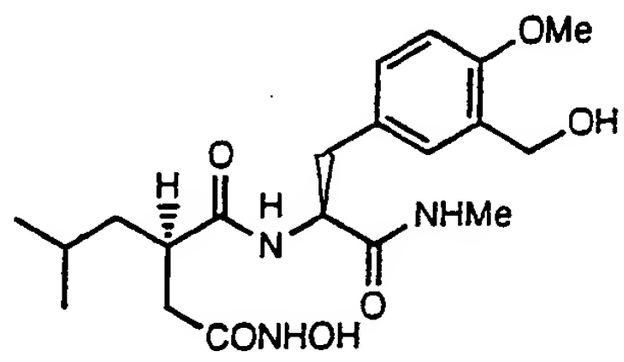
[4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-(1-(2-methoxycarbonyl)-ethene)-4-methoxy-phenylalanine-N-methylamide (300 mg, 0.60 mmol) was dissolved in DCM (3 mL) and TFA (3 mL) added dropwise and the mixture stood at 4° overnight. Solvent removal gave the acid as a solid which was recrystallised from ethanol/diethyl ether (m.p. 176 -177°). This crude acid was coupled with O-benzylhydroxylamine in the presence of pentafluorophenol as described in example 24b to give the benzhydroxamate (200 mg, 0.36 mmol, 61%): ^{1}H-NMR; δ ($CDCl_3$), 7.90 (1H, d, J=16.1 Hz, $ArC\underline{H}CHCO_2Me$), 7.36 (6H, m, Aryl-H and Ph), 7.18 (1H, dd, J=6.4, 2.1 Hz, Aryl-H), 6.80 (1H, d, J=8.5 Hz, Aryl-H3), 6.69 (1H, bs, $CON\underline{H}$), 6.52 (1H, d, J=16.1 Hz, $ArCHC\underline{H}CO_2Me$), 6.28 (1H, m, $CON\underline{H}Me$), 4.87 (2H, s, $OC\underline{H}_2Ph$), 4.55 (1H, q, J=7.5 Hz, $NHC\underline{H}CO$), 3.81 (3H, s, $OC\underline{H}_3$), 3.78 (3H, s, $CO_2C\underline{H}_3$), 3.02 (2H, m, CH_2Ar), 2.71 (3H, d, J=4.7 Hz, $CONHC\underline{H}_3$), 2.71 (2H, m, $C\underline{H}_2CO_2{}^tBu$), 2.18 (1H, m, $^iBuC\underline{H}$), 1.44 (2H, m, $(CH_3)_2CHC\underline{H}_2$), 1.20 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 0.85 (3H, d, J=6.3 Hz, $CH(C\underline{H}_3)_2$), and 0.80 (3H, d, J=6.3 Hz, $CH(C\underline{H}_3)_2$).

c) [4-(N-Hydroxyamino)-2R-isobutyl-succinyl]-L-3-(1-(2-methoxycarbonyl)-ethyl)-4-methoxy-phenylalanine-N-methylamide

[4-(N-Benzyloxyamino)-2R-isobutyl-succinyl]-L-3-(1-(2-methoxycarbonyl)-ethene)-4-methoxy-phenylalanine-N-methylamide (200 mg, 0.36 mmol) was hydrogenated as described in example 10c to yield the title compound (73 mg, 43%): M.p. 173°: Found: C, 59.34, H, 7.57, N, 8.89%. $C_{23}H_{35}N_3O_7$ requires C, 59.34, H, 7.58, N, 9.03%: ν_{max} (KBr), 3300, 3000, 1750, and 1640 cm^{-1}: ^{1}H-NMR; δ (Methanol-d_4), 6.98 (2H, m, Aryl-H), 6.79 (1H, d, J=8.2 Hz, Aryl-H3), 4.43 (1H, dd, J=6.5, 2.2 Hz, $NHC\underline{H}CO$), 3.75 (3H, s, $OC\underline{H}_3$), 3.60 (3H, s, $CO_2C\underline{H}_3$), 3.03 (1H, dd, J=6.4, 7.4 Hz, CH_2Ar), 2.85 - 2.60 (7H, m + s, $2XC\underline{H}_2$ and $CONHC\underline{H}_3$), 2.52 (2H, m, $C\underline{H}_2CO_2{}^tBu$), 2.06 (2H, bm), 1.05 (1H, m, $(CH_3)_2C\underline{H}CH_2$), 0.80 (3H, d, J=6.3 Hz, $CH(C\underline{H}_3)_2$), and 0.76 (3H, d, J=6.3 Hz, $CH(C\underline{H}_3)_2$): ^{13}C-NMR; δ (Methanol-d_4), 177.1, 175.5, 174.0, 170,6, 157.7, 131.7, 130.4, 129.8, 129.5, 111.3, 56.3, 55.8, 52.0, 42.7, 42.4, 37.9, 35.0, 27.1, 26.8, 26.3, 23.5 and 22.3.

Example 26

[4-(N-Hydroxyamino)-2R-isobutyl-succinyl]-L-3-(hydroxymethyl)-4-methoxy-phenylalanine-N-methylamide (BB 792).



a) [4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-(hydroxymethyl)-4-methoxy-phenylalanine-N-methylamide.

[4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-(1-(2-methoxycarbonyl)-ethene)-4-methoxy-phenylalanine-N-methylamide (see example 25a, 300 mg, 0.6 mmol) was dissolved in methanol, cooled to -78° and a stream of ozone passed through for 40 minutes. The solution was warmed to 0° and argon bubbled through for 15 minutes then sodium borohydride (57 mg, 1.5 mmol) added and the soution warmed to room temperature over an hour. Water was added to quench excess borohydride then the solvents removed under reduced pressure and the residue taken up in DCM. The organic layer was washed with brine then dried over magnesium sulphate then the solvent removed to leave the title compound as a white solid (240mg, 0.54 mmol, 90%): ^{1}H-NMR; δ ($CDCl_3$), 7.18 (1H, d, J= 2.1 Hz, Aryl-H), 7.03 (1H, dd, J=8.4, 2.1 Hz, Aryl-H), 6.75 (3H, m, CONHCH, Aryl-H and CONHMe), 4.60 (3H, bm, CH_2OH and NHCHCO), 3.76 (3H, s, OCH_3), 3.30 (1H, bs, OH), 2.99 (2H, m, CH_2Ar), 2.66 (3H, d, J=4.7 Hz, $CONHCH_3$), 2.62 - 2.23 (3H, m, $CH_2CO_2{}^tBu$ and ^{i}BuCH), 1.38 (11H, s + m, $C(CH_3)_3$ and $(CH_3)_2CHCH_2$), 1.20 (1H, m, $(CH_3)_2CHCH_2$), 0.83 (3H, d, J=6.3 Hz, $CH(CH_3)_2$), and 0.76 (3H, d, J=6.3 Hz, $CH(CH_3)_2$).

b) [4-(N-Benzyloxyamino)-2R-isobutyl-succinyl]-L-3-(hydroxymethyl)-4-methoxy-phenylalanine-N-methylamide.

[4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-(hydroxymethyl)-4-methoxy-phenylalanine-N-methylamide (249 mg, 0.53 mmol) was treated with TFA/DCM as described in example 25b to give the acid which was purified by recrystallisation from ethyl acetate/hexane (m.p. 146 -147°, 200mg, 0.50 mmol, 94%). This acid was coupled to O-benzylhydroxylamine as

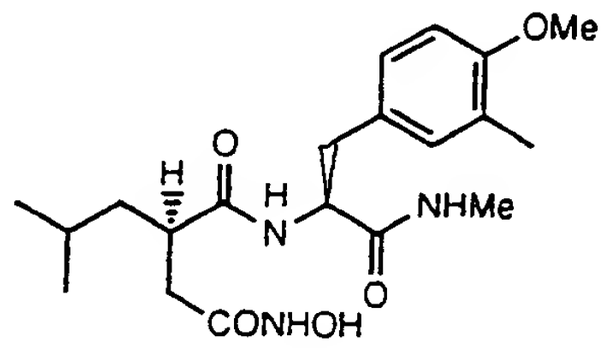
described in example 24b to yield the benzhydroxamate (130mg, 0.27 mmol, 54%): ^{1}H-NMR; δ (DMSO-d_6), 11.00 (1H, s, CONHOH), 8.05 (1H, bd, NHCH), 7.81 (1H, m, CONHMe), 7.40 (5H, s, Ph), 7.23 (1H, bs, Aryl-H), 7.03 (1H, bm, Aryl-H), 6.80 (1H, m, Aryl-H), 4.75 (2H, bs, OCH_2Ph), 4.40 (3H, bm, CH_2OH and NHCHCO), 3.72 (3H, s, OCH_3), 3.00 - 2.60 (2H, m, CH_2Ar), 2.60 - 2.40 (5H, m, $CH_2CO_2{}^tBu$ and $CONHCH_3$), 2.05 (1H, m, ^{i}BuCH), 1.27 (2H, m, $(CH_3)_2CHCH_2$), 0.98 (1H, m, $(CH_3)_2CHCH_2$), 0.78 (3H, bd, $CH(CH_3)_2$), and 0.73 (3H, d, $CH(CH_3)_2$).

c) [4-(N-Hydroxyamino)-2R-isobutyl-succinyl]-L-3-(hydroxymethyl)-4-methoxy-phenylalanine-N-methylamide.

[4-(N-Benzyloxyamino)-2R-isobutyl-succinyl]-L-3-(hydroxymethyl)-4-methoxy-phenylalanine-N-methylamide (130 mg, 0.27 mmol) was hydrogenated as described in example 10c to yield the title compound (42mg, 0.10 mmol, 38%): ^{1}H-NMR; δ (Methanol-d_4), 7.19 (1H, s, Aryl-H), 7.06 (1H, dd, J=6.2, 2.1 Hz, Aryl-H), 6.80 (1H, m, Aryl-H), 4.55 (2H, s, CH_2OH) 4.44 (1H, dd, J=6.3, 2.3 Hz, NHCHCO), 3.76 (3H, s, OCH_3), 3.10 - 2.81 (2H, m, CH_2Ar), 2.65 (4H, s + m, ^{i}BuCH and $CONHCH_3$), 2.22 - 2.04 (2H, m, $CH_2CONHOH$), 1.38 (2H, m, $(CH_3)_2CHCH_2$), 1.08 (1H, m, $(CH_3)_2CHCH_2$), 0.81 (3H, d, J=6.5 Hz, $CH(CH_3)_2$), and 0.75 (3H, d, J=6.5 Hz, $CH(CH_3)_2$): ^{13}C-NMR; δ (Methanol-d_4), 176.6, 173.8, 156.9, 130.2, 129.9, 129.6, 110.8, 60.1, 56.0, 55.5, 42.2, 42.0, 37.7, 36.4, 26.4, 26.0 and 23.2.

Example 27

[4-(N-Hydroxyamino)-2R-isobutyl-succinyl]-L-3-methyl-4-methoxy-phenylalanine-N-methylamide (BB 804).



a) [4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-methyl-4-methoxy-phenylalanine-N-methylamide.

[4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-(1-(2-methoxycarbonyl)-

ethene)-4-methoxy-phenylalanine-N-methylamide (see example 25a, 300 mg, 0.6 mmol) was dissolved in methanol, cooled to -78° and a stream of ozone passed for 30 minutes. Dimethyl sulphide (56mg, 0.9 mmol) in DCM (10 mL) was added and the mixture warmed to 0°. The solvents were removed under vacuum the residue dissolved in DCM and washed with water. The organic layer was dried over magnesium sulphate, filtered and the solvent removed to leave a crude solid which was purified by recrystallisation from ethyl acetate (200mg, 0.46 mmol, 77%): ^{1}H-NMR; δ ($CDCl_3$), 6.97 (2H, bs, Aryl-H), 6.70 (1H, d, J=8.8 Hz, Aryl-H), 6.46 (1H, d, J=8.7 Hz, CONHCH), 6.26 (1H, bm, CONHMe), 4.51 (1H, q, J=7.2 Hz, NHCHCO), 3.77 (3H, s, OCH_3), 3.00 (2H, m, CH_2Ar), 2.68 (3H, d, J=4.7 Hz, $CONHCH_3$), 2.67 - 2.28 (3H, m, $CH_2CO_2{}^tBu$ and ^iBuCH), 2.15 (3H, s, Aryl-CH_3), 1.41 (11H, s + m, $C(CH_3)_3$ and $(CH_3)_2CHCH_2$), 1.17 (1H, m, $(CH_3)_2CHCH_2$), 0.83 (3H, d, J=6.3 Hz, $CH(CH_3)_2$), and 0.78 (3H, d, J=6.3 Hz, $CH(CH_3)_2$).

b) [4-(N-Benzyloxyamino)-2R-isobutyl-succinyl]-L-3-methyl-4-methoxy-phenylalanine-N-methylamide.

[4-tert-Butoxy-2R-isobutyl-succinyl]-L-3-methyl-4-methoxy-phenylalanine-N-methylamide (200mg, 0.46 mmol) was deprotected with TFA as described in 25b to yield the acid (110mg, 0.29 mmol, 63%) which was coupled with O-benzylhydroxylamine as described in example 24b to yield the title compound as a white crystalline solid (70 mg, 0.14 mmol, 56%): ^{1}H-NMR; δ ($CDCl_3$), 8.54 (1H, bs, CONHOBn), 7.37 (5H, bs, Ph), 6.98 (2H, m, Aryl-H), 6.73 (1H, d, J=8.9 Hz, Aryl-H), 6.46 (1H, bd, CONHCH), 5.88 (1H, bm, CONHMe), 4.87 (2H, s, OCH_2Ph), 4.47 (1H, dd, J=7.7, 6.4 Hz, NHCHCO), 3.79 (3H, s, OCH_3), 3.08 - 2.94 (2H, m, CH_2Ar), 2.70 (4H, d + m, J=4.7 Hz, $CONHCH_3$ and $CH_2CO_2{}^tBu$), 2.25 (1H, m, $CH_2CO_2{}^tBu$), 2.18 (3H, s, Aryl-CH_3), 1.46 (2H, m, $(CH_3)_2CHCH_2$), 1.23 (1H, m, $(CH_3)_2CHCH_2$), 0.89 (3H, d, J=6.4 Hz, $CH(CH_3)_2$), and 0.78 (3H, d, J=6.4 Hz, $CH(CH_3)_2$).

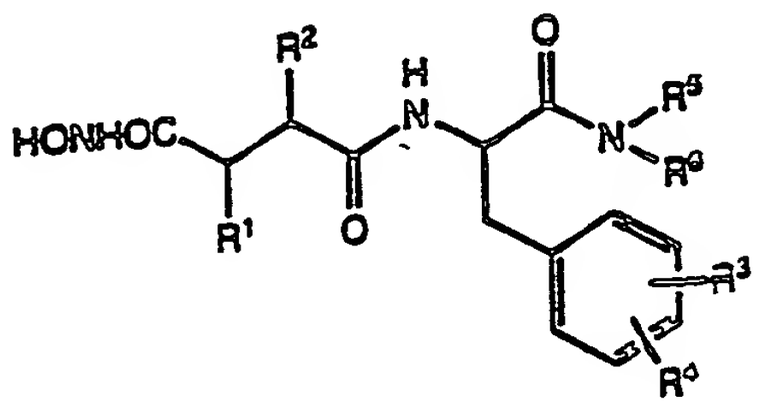
c) [4-(N-Hydroxyamino)-2R-isobutyl-succinyl]-L-3-methyl-4-methoxy-phenylalanine-N-methylamide

[4-(N-Benzyloxyamino)-2R-isobutyl-succinyl]-L-3-methyl-4-methoxy-phenylalanine-N-methylamide (70 mg, 0.14 mmol) was hydrogenated as described in example 10c to give the hydroxamic acid (40 mg, 0.1 mmol, 71%): m.p. 170 -171°: ^{1}H-NMR; δ (Methanol-d_4), 10.44 (1H, s, CONHOH), 8.81 (1H, s, CONHOH), 8.00 (1H, bd, CONHCH), 7.88 (1H, bm, CONHMe), 6.97 (2H, m, Aryl-H), 6.79 (1H, d, J=8.9 Hz, Aryl-H), 4.31 (1H, m, NHCHCO), 3.75 (3H,

s, OCH_3), 2.94 (1H, m, CH_2Ar), 2.78 - 2.43 (5H, bm, $CONHCH_3$, CH_2Ar and $CH_2CO_2{}^tBu$), 2.13 (3H, s, Aryl-CH_3), 2.13 - 1.88 (2H, m, $CH_2CO_2{}^tBu$ and ^tBuCH), 1.25 (2H, m, $(CH_3)_2CHCH_2$), 0.97 (1H, m, $(CH_3)_2CHCH_2$), 0.78 (3H, d, J=6.4 Hz, $CH(CH_3)_2$), and 0.72 (3H, d, J=6.4 Hz, $CH(CH_3)_2$)

CLAIMS

1. A compound of general formula I



I

Wherein :

R^1 is hydrogen, C_1 - C_6 alkyl, phenyl, substituted phenyl, phenyl(C_1 - C_6 alkyl), or heterocyclyl;

or R^1 is ASO_nR^7

wherein A represents a C_1 - C_6 hydrocarbon chain, optionally substituted with one or more C_1 - C_6 alkyl, phenyl or substituted phenyl groups

n = 0,1,2;

R^7 is C_1 - C_6 alkyl, phenyl, substituted phenyl, phenyl (C_1-C_6 alkyl), heterocyclyl, (C_1 - C_6 alkyl)acyl, thienyl or phenacyl;

R^2 is hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, phenyl (C_1 - C_6alkyl) or cycloalkyl(C_1 - C_6 alkyl);

R^3 and R^4 are selected from hydrogen, halogen, cyano

amino, amino(C_1 - C_6)alkyl, amino di(C_1 - C_6)alkyl, amino(C_1 - C_6)alkylacyl, aminophenacyl, amino (substituted) phenacyl, amino acid or derivative thereof, hydroxy, oxy(C_1 - C_6)alkyl, oxyacyl, formyl, carboxylic acid, carboxamide, carboxy(C_1 - C_6) alkylamide, carboxyphenylamide, carboxy(C_1 - C_6) alkyl, hydroxy(C_1 - C_6)alkyl, (C_1 - C_6)alkyloxy(C_1 - C_6) alkyl or acyloxy(C_1 - C_6)alkyl, (C_1 - C_6)alkylcarboxylic acid, (C_1-C_6) alkylcarboxy(C_1 - C_6) alkyl, amino (C_{1-6})alkylacyl carboxylic acid or amino (C_{1-6})alkylacyl (C_{1-6}) alkylcarboxylate;

or R^3 is OCH_2COR^8 and R^4 is hydrogen;

wherein R^8 is hydroxyl, C_1 - C_6 oxyalkyl, C_1 - C_6 oxyalkylphenyl, amino, C_1 - C_6 aminoalkyl, C_1 - C_6 aminodialkyl, C_1 - C_6 aminoalkylphenyl, an amino acid or derivative thereof;

or R^3 is $OCH_2CH_2OR^9$ and R^4 is hydrogen;

wherein R^9 is C_1 - C_6 alkyl, C_1 - C_6 alkylphenyl, phenyl, substituted phenyl, (C_1 - C_6 alkyl)acyl, or phenacyl;

or R^3 is OCH_2CN and R^4 is hydrogen;

R^5 is hydrogen or C_1 - C_6 alkyl, or (C_1 - C_6) alkylphenyl;

R^6 is hydrogen or methyl;

or a salt thereof;

specifically excluded are compounds wherein:

$R^3 = R^4$ = hydrogen

or $R^3 = R^4$ = hydroxy

or R^3 = hydrogen and R^4 = oxybenzyl

or R^3 = hydrogen and R^4 = oxy(C_1 - C_6 alkyl);

or a salt thereof.

2. A compound as claimed in Claim 1, in which the chiral centre adjacent to the sustituent R^2 has R stereochemistry.

3. A compound as claimed in Claim 1, in which the chiral centre adjacent to the substituted benzyl group has S stereochemistry.

4. A compound as claimed in Claim 1, in which the chiral centre adjacent to R^1 has S stereochemistry.

5. A compound as claimed in Claim 1 in which R^1 represents a hydrogen atom or a C_1 -C_4 alkyl group, or an arylthiomethyl group or a thiophenethiomethyl group.

6. A compound as claimed in Claim 1 in which R^2 represents a C_3 -C_6 alkyl group.

7. A compound as claimed in Claim 1 in which R^3 represents cyano, aminoalkylacyl, amino (C_{1-6})alkylacylcarboxylic acid, amino (C_{1-6})alkylacyl

(C_{1-6})alkylcarboxylate or OCH_2COR^8 and R^4 is hydrogen;

Wherein R^8 is as defined above.

8. A compound as claimed in Claim 1 in which R^5 represents a C_{1-5} alkyl group.

9. A compound as claimed in Claim 1 in which R^6 represents a hydrogen atom.

10. [4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxylicacid) phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxy-N-methylamide)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxy-beta-alanine)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethylcarboxyglycine)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxymethyl carboxy-N-benzylamide)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-cyano) phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-acetamido)phenylalanine-N-methylamide;

[4-(N-Hydroxyamino)-2R-isobutylsuccinyl]-L-(4-oxy-methylcarboxamide)-phenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio methyl succinyl]-L-(4-N-acetylamino)-phenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-methylsuccinyl]-L-(4-N-methylsuccinylamide)-phenyl-alanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthio-methyl)-succinyl]-L-(4-N-(methylsuccinylamide)-phenyl-alanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(4-aminophenylthio-methyl)-succinyl]-L-(4-N-(4-(4-oxobutanoic acid)-aminophenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenyl-thiomethyl)-succinyl]-L-(4-N-(methylsuccinylamido)-phenylalanine-N-methylamide;

[4-(N(hydroxyamino)-2R-isobutyl-3S-(4-hydroxyphenyl-thiomethyl)-succinyl]-L-(4-N-(4-(4-oxobutanoic acid)-aminophenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-methyl)-succinyl]-L-4-(oxymethylcarboxymethyl)-phenyl-alanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-methyl)-succinyl]-L-(4-N-(oxymethylcarboxylic acid)-phenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-methyl)-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-(2-thienylthio-methyl)-succinyl]-L-4-(oxymethylcarboxyglycine)-phenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycyl methyl ester)-phenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutyl-(3S-methyl-succinyl]-L-4-(oxymethylcarboxyglycine)-phenylalanine-N-methyl-amide;

[4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-4-(oxy-methylnitrile)-phenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-(1-(2-methyoxycarbonyl)-ethyl)-4-methoxyphenylalanine-N-methylamide;

[4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-(hydroxy-methyl)-4-methoxyphenylalanine-N-methylamide; or

[4-(N-hydroxyamino)-2R-isobutylsuccinyl]-L-3-methyl-4-methyoxyphenylalanine-N-methylamide.

or a salt of one of them.

11. A compound as claimed in Claim 1 for use in human or veterinary medicine.

12. The use of a compound as claimed in Claim 1 in the preparation of an agent for use in the management of disease involving collagen breakdown.

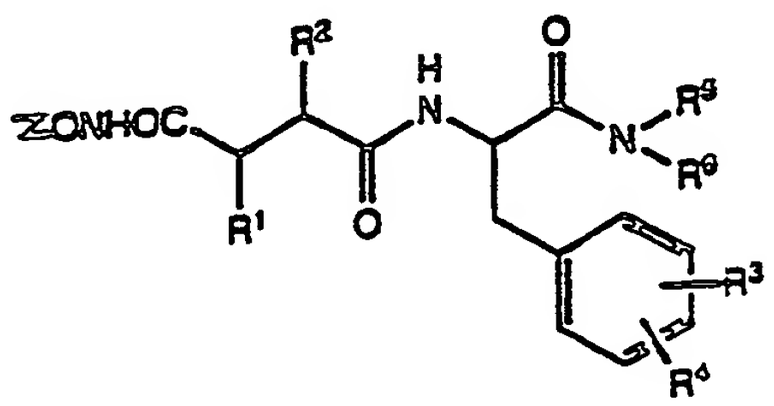
13. A pharmaceutical or veterinary composition comprising a compound as claimed in Claim 1 together with a pharmaceutically and/or veterinarily acceptable carrier.

14. A composition as claimed in Claim 13 in unit dosage form and comprising 10-500mg of a compound of formula I.

15. A method for the treatment or prophylaxis of disease involving collagen breakdown, the method comprising administering to a patient an effective amount of a compound as claimed in claim 1.

16. A process for the preparation of a compound of formula I comprising:

a) deprotection of a compound of formula II,

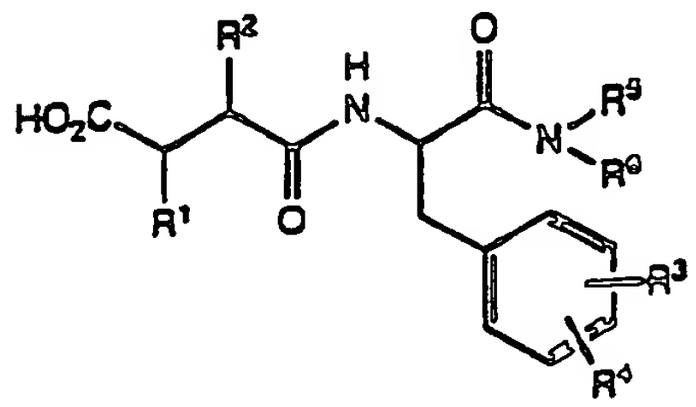


II

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined for

general formula I and Z represents a protective group;
or

b) reacting a compound of formula III:

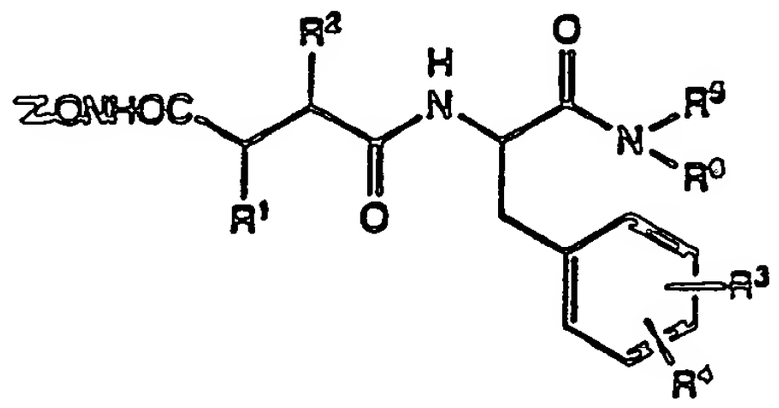


III

wherein: R^1, R^2, R^3, R^4, R^5 and R^6 are as defined for general formula I, with hydroxylamine or a salt thereof; and

C) optionally after step (a) or step (b) converting a compound of general formula I into another compound of general formula I.

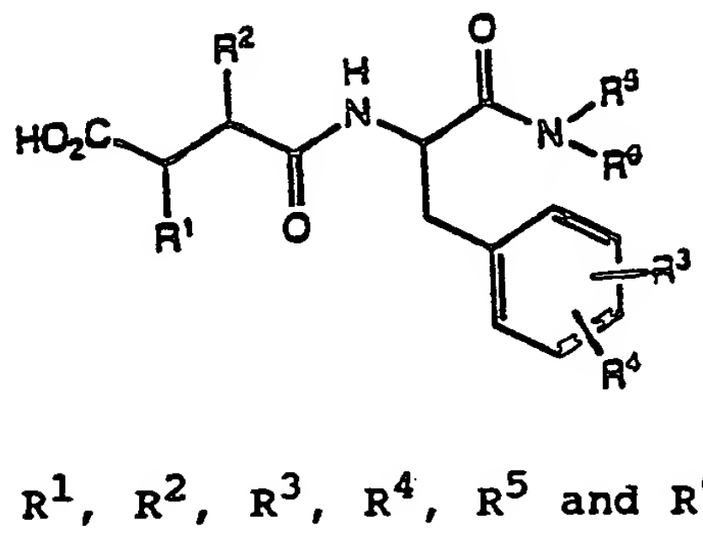
17. A compound of general formula II,



II

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined for general formula I and Z is a protective group.

18. A compound of general formula III,



III

wherein R^1, R^2, R^3, R^4, R^5 and R^6 are as defined for general formula I

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 92/00230

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07C259/06; C07C317/44; C07C323/52; C07D333/34
A61K31/165; C07C237/22

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07C ; C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0 214 639 (G. D. SEARLE & CO.) 18 March 1987 * abstract , page 20 - page 50 * & US,A,4 599 361 8 July 1986 cited in the application	1-6, 11-16,18
A	WO,A,9 005 719 (BRITISH BIO-TECHNOLOGY LIMITED) 31 May 1990 cited in the application see page 26 - page 72; claims 1-8	1-6, 11-15
A	WO,A,9 005 716 (BRITISH BIO-TECHNOLOGY LIMITED) 31 May 1990 cited in the application see page 31 - page 86; claims 1-7,13-17	1-6, 11-18
A	EP,A,0 274 453 (LABORATOIRE ROGER BELLON) 13 July 1988 see abstract	1,11-13, 15

-/--

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
11 MARCH 1992	31 MAR 1992
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	RUFET J.

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0 236 872 (F. HOFFMANN - LA ROCHE & CO.) 16 September 1987 see claims 1,24-28 ---	1-6, 11-13,15

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9200230 SA 56204

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 11/03/92

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		AU-B-	588362	14-09-89
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